SCHOOL OF MEDICINE

DEPARTMENT OF PHARMACOLOGY PROGRAM

SELF-STUDY

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*The organization of this report closely follows the Self-Study Format of the Graduate School of the University of Washington. *See Tab 2.*

I. Context

A. Name of Unit Authorized to Offer Degrees: Department of Pharmacology

B. Applicable School: School of Medicine

C. Exact Titles of Degrees Offered: Master of Science and Doctor of Philosophy

D. Historical Perspective

Pharmacology is broadly defined as the study of the interactions of living cells and organisms with the molecules they encounter in their environment. Areas of active research include evaluation of the effects of drugs and environmental chemicals on humans and animals, the study of the actions of hormones, neurotransmitters, and other physiological regulators on individual cells, and examination of the detailed molecular structure of cellular constituents that play critical roles in cellular regulation and drug interactions. Modern research in pharmacology applies experimental methods derived from disciplines that range from clinical medicine to biophysics, genetics, biochemistry, and molecular biology to provide a detailed understanding of drug action and cellular regulation at many different levels of inquiry: the human patient, the experimental animal, the individual cell, the proteins that are the cellular mediators of drug and hormone actions, and the genes that specify their structure.

The Department of Pharmacology at the University of Washington began in 1946 as one of the founding departments of the School of Medicine. Dr. James Dille, its first Chair and an Assistant Dean of the School of Medicine, led the department to national prominence in the 1950's and 1960's. Research in the department at that time emphasized neuropharmacology, cardiovascular pharmacology, and toxicology. Most investigations focused on the actions of drugs and environmental chemicals on experimental animals and organ systems. During the 1970's, revolutionary advances in cellular and molecular biology began to have a profound impact in pharmacology. Receptors for hormones, neurotransmitters, and drugs were identified and purified from tissues, second messenger pathways were recognized as major substrates for drug action, and the field of cellular signal transduction became a major area of research activity. To respond to these dramatic advances, the University of Washington School of Medicine appointed Dr. Edwin Krebs as Chair of the Department of Pharmacology in 1977 and provided support for expansion and development of research programs in molecular pharmacology and cellular signal transduction. In the subsequent decade, the department built firmly around the

themes of molecular pharmacology and cellular signal transduction and is now recognized as one of the pre-eminent departments of pharmacology in the U.S. Surveys compiled by the Association for Medical School Pharmacology, the society of pharmacology chairs, show that the Department of Pharmacology at the University of Washington is among the top departments in total research support, research support per full-time faculty member, number of postdoctoral fellows, and number of graduate students, although the number of full-time faculty members is below the national average. The strong research programs and active research environment in the department provide a firm basis for an excellent graduate training program.

The Department of Pharmacology at the University of Washington has maintained an active Ph.D. degree program since the founding of the department in 1946. In 1951, the graduate program had seven students. The number of students has increased steadily to the current average of 36. In 1958, the Department of Pharmacology at the University of Washington was awarded the first NIH Training Grant in Pharmacology. Since that time, the graduate training program in the Department of Pharmacology has been continuously supported by an NIH Training Grant with the exception of a brief lapse in the early 1970's. Students in the Department of Pharmacology are supported through several training grants and the faculty places a high priority on maintaining a firmly funded, academically outstanding graduate training program.

II. Unit Administration, Roles, Responsibilities, and Measures of Success

Administration of the Department of Pharmacology

The administration of the Department of Pharmacology is the responsibility the Chair, assisted by an Administrator. The Chair is responsible for administrative and policy decisions concerned with academic matters. The Administrator is responsible for the day-to-day operation of the department. The Chair holds regular monthly meetings with members of the faculty. These meetings provide an opportunity for an exchange of information of general interest and discussion of issues that may impact members of the department. Policy decisions are made based on the advice of the faculty presented at these meetings. Academic programs are administered by faculty committees under the direction of the Chair.

Departmental Faculty Committees

Committee on Graduate and Pharmacy Education

This committee includes the heads of the three subcommittees (Graduate Program Advising, Graduate Admissions, and Graduate Student Funding) which oversee the graduate program. Each subcommittee has a specific mission and the members operate on an interdependent basis (i.e., all members vote on admissions, graduate policy changes, etc.).

Graduate Admissions Subcommittee

This committee oversees recruitment and selection of graduate students.

Graduate Program Advisory Subcommittee

This faculty committee is headed by the Graduate Program Advisor. This faculty member's role is to: 1) acquire and maintain familiarity with the policies and procedures of the Graduate School and to ensure that these policies and procedures are communicated to faculty and students in the department, 2) maintain department-Graduate School liaison (i.e., to communicate with the Dean of the Graduate School regarding selection of students' supervisory chairs and committees), 3) advise first-year students prior to their selection of a thesis mentor, 4) give quarterly reports to the faculty on each student's progress, and 5) oversee administration of general examinations.

Graduate Student Funding Subcommittee

This committee, consisting of faculty members and the Administrator, is responsible for maintaining records on past and current funding. The committee develops comparative salary data within the school and from other pharmacology departments for use in determining departmental graduate student stipend levels. This committee advises the Chair on student funding and assignment to training grant positions.

Committee on Medical Education

This committee is composed of three members, two of whom chair the two pharmacology courses taught as part of the medical student curriculum (Human Biology 543 and 564). The remaining member is the department's representative to the Medical Scientist Training Program (an NIH-sponsored training program which supports students training as M.D./Ph.D.s). This member also coordinates the ISMS (Independent Study in Medical Sciences) Program that provides medical students an opportunity to be involved in research projects of Pharmacology faculty.

The ***Seminar Chair*** is responsible for the administrative organization of the departmental seminar program.

Faculty Search Committees are appointed ad hoc by the Chair for each open position in the department. The search criteria are developed in consultation with the full faculty of the department. The search committees then screen applicants, invite candidates for visits, and organize the consideration of candidates by the faculty. Appointments are made based on a consensus vote of the faculty of the department.

A. Academic Roles of the Department

Education in pharmacology for health science professional students

The faculty members of the department organize and teach separate course series in general pharmacology for medical, dental, and pharmacy students.

Graduate education and research training in pharmacology

The department has an active educational and research-training program for graduate students seeking the Ph.D. degree in Pharmacology. The program includes introductory courses in general pharmacology, research seminar courses in specific topics in pharmacology and related interdisciplinary subjects, research conferences and journal clubs, and intensive laboratory training in modern biomedical science. Graduates are expected to become leaders in research, teaching, and scientific administration in universities, research institutes, biotechnology companies, pharmaceutical companies, and governmental agencies.

For graduate students who decide after entering the program that a research career as a principal investigator is not optimal for them, the Department of Pharmacology grants a M.S. degree in Pharmacology based on successful completion of basic course work in Pharmacology and related disciplines and a research project that is presented as a Master's thesis and defended before a faculty committee.

The department also provides research-training experiences for undergraduates through its research laboratory course for independent study, Pharmacology 499.

Graduate and undergraduate education and research training in interdisciplinary programs related to pharmacology

The faculty members of the department participate actively in interdisciplinary undergraduate and graduate teaching and research training programs related to pharmacology as teachers, research mentors, and program leaders, including the Graduate Program in Neurobiology & Behavior, the undergraduate Neurobiology Program, and the Molecular & Cellular Biology Program. For further information on these programs, please visit their websites:
Graduate Program in Neurobiology & Behavior: http://depts.washington.edu/behneuro/
Molecular & Cellular Biology Program: http://depts.washington.edu/mcb/

Research in pharmacology and related interdisciplinary subjects, including neurobiology and cellular regulation

The department has internationally recognized research programs in molecular pharmacology, neuropharmacology, molecular and cellular neurobiology, cellular regulation and development, and drug metabolism and toxicology. Faculty members generate substantial extramural grant funding to fully support their research activities and the research training of graduate students.

Administrative leadership of the School of Medicine and the University of Washington

Faculty members of the department play essential roles as academic leaders through service on school and university committees and in appointed leadership positions.

B. Departmental Opportunities in Education and Research

Educational Programs and Opportunities

Pharmacology

Pharmacology is a bridging discipline in the biomedical sciences. In its educational programs for health science professional students, it bridges basic science to clinical medicine and pharmacy practice through its focus on the basic science of drug action. This central position in the biomedical sciences provides numerous educational opportunities. The Department of Pharmacology teaches year-long courses in basic pharmacology to pharmacy students and graduate students in pharmacology, medicinal chemistry, and pharmaceutics. The faculty has developed a series of eight graduate seminar courses in specialty areas, which are taught to graduate students in pharmacology, the interdisciplinary graduate programs and other basic science departments. The Department of Pharmacology teaches two separate courses in

pharmacology in the second year of the Medical School's curriculum—one focussing on basic principles of pharmacology, cardiovascular and autonomic pharmacology, and anti-bacterial, anti-viral, and anti-cancer therapeutics and one on neuropharmacology. Additional topics in pharmacology are taught within the organ-system courses in the second year of the Medical School's curriculum. The department also teaches a two-quarter course in pharmacology to dental students in the second year of the Dental School's curriculum.

Interdisciplinary teaching

In addition to its educational programs in pharmacology, the Department of Pharmacology participates actively in undergraduate level and graduate level teaching in interdisciplinary programs. It teaches a one-quarter course on Neuropharmacology for undergraduates in the Neurobiology Program. It teaches a module on Cellular Signal Transduction from Plasma Membrane to Nucleus for a broad range of first-year graduate students in Conjoint 532. Faculty members from the department also teach extensively in courses of the Graduate Program in Neurobiology & Behavior.

Training Programs Funded by the National Institutes of Health

Faculty members of the Department of Pharmacology participate in several graduate and postdoctoral training programs funded by the National Institutes of Health. All of the faculty participate in the Pharmacological Sciences Training Program headed by Dr. Wendell Nelson of the Department of Medicinal Chemistry in the School of Pharmacy. This training program and several others with departmental participation are described below.

Pharmacological Sciences Training Program. Three departments participate in this training program – Pharmacology in the School of Medicine and Medicinal Chemistry and Pharmaceutics in the School of Pharmacy. The administrative base is in Medicinal Chemistry, with Dr. Wendell Nelson as Director. Fourteen faculty members of the Department of Pharmacology participate as preceptors on this training grant. These are Drs. Bajjalieh, Beavo, Catterall, Chavkin, Dorsa, Juchau, McKnight, Moon, Nathanson, Storm, Stella, Tempel, Vincenzi, and Wang. Currently seven of our 33 graduate students are supported by this training grant.

Molecular and Cellular Biology Training Program. Eight departments participate in this training program – Biochemistry, Pathology, Physiology/Biophysics, Pharmacology, Microbiology, Biological Structure, Zoology and Botany. The administrative base is in Biochemistry, with Dr. David Kimelman as Director. Thirteen Pharmacology faculty members participate as preceptors on this training grant. They are Drs. Bajjalieh, Beavo, Catterall,

Chavkin, Dorsa, Juchau, Krebs, McKnight, Moon, Omiecinski, Stella, Storm, Tempel, Wang and Watson. Four graduate students in Pharmacology are currently supported by this training grant.

Cardiovascular Pathology Training Program. The administrative base is in the Department of Pathology. Six departments provide preceptors for this program: Pathology, Pharmacology, Biochemistry, Medicine, Surgery, Microbiology, and Biological Structure. Three faculty members of the Department of Pharmacology participate as preceptors on this training grant. These are Drs. Beavo, Catterall, and Nathanson.

Environmental Pathology Training Program. Four departments participate in this training program – Pharmacology, Pathology, Environmental Health, and Fisheries. The administrative base is in Pathology, with Dr. Nelson Fausto as Director. Two members of the Department of Pharmacology participate as preceptors on this training grant. These are Drs. Juchau and Omiecinski. Currently one graduate student is supported by this training grant.

Medical Scientist Research Training Program. Six departments participate in this training program – Biochemistry, Pharmacology, Physiology & Biophysics, Microbiology, Biological Structure, and Pathology. The administrative base is in the office of the Dean of the School of Medicine and in the Department of Pathology, with Dr. Larry Loeb as Director. All faculty members of the Department of Pharmacology are participants in this program.

Developmental Biology Training Program. Nine departments participate in this training program: Pharmacology, Biochemistry, Genetics, Zoology, Botany, Microbiology, Otolaryngology, Pediatrics and Biological Structure. The administrative base is in the Department of Zoology, with Dr. Lynn Riddiford as Director. Two members of our department, Drs. Moon and Nathanson, participate as a preceptors on this training program. Currently, one of our graduate students is supported by this grant.

Vision Sciences Training Program. Administrative base is in the Department of Biological Structure, with Dr. Anita Hendrickson as Director. Seven departments participate in this training grant. These are Psychology, Ophthalmology, Biological Structure, Physiology/Biophysics, Biochemistry, Pharmacology and Obstetrics & Gynecology. Two members of our department, Drs. Beavo and Palczewski, participate as preceptors in this training program.

Dental Scientist Training Program. Administrative base is in the Dean's Office of the School of Dentistry. Fourteen departments participate in this training program. These are Endodontics,

Periodontics, Oral Medicine, Prosthodontics/Restorative Dentistry, Orthodontics, Oral Pathology, Biological Structure, Biochemistry, Microbiology/Immunology, Pharmacology, Pathology, Physiology/Biophysics, Epidemiology, and Psychology. All faculty members of the Department of Pharmacology are listed as potential preceptors for trainees on this grant.

Molecular Neurobiology Training Program. This training program is based in the Department of Pharmacology with Dr. William Catterall as Director. Three departments participate in this training effort. These are Pharmacology, Physiology & Biophysics, and Biochemistry. Pharmacology faculty members participating as preceptors are Drs. Bajjalieh, Beavo, Catterall, Chavkin, Dorsa, McKnight, Nathanson, Storm, and Tempel. Two students are supported by this grant at present.

Molecular Pharmacology of Abused Drugs Training Program. This predoctoral and postdoctoral training program is based in the Department of Pharmacology with Dr. Charles Chavkin as director. Pharmacology, Physiology & Biophysics, Anesthesiology, Medicinal Chemistry and Biochemistry. Participating faculty members include Drs. Catterall, Chavkin, Dorsa, Mackie, McKnight, Nathanson, Stella, Storm, Tempel, and Terman. Currently, two of our students are supported by this training program.

Systems and Integrative Biology Training Program. Administrative base is in the Department of Physiology & Biophysics, with Dr. Mark Binder as Director. Participating departments in the Graduate Neuroscience Training Program are Physiology & Biophysics, Pharmacology, Zoology, Biological Structure and Psychology. Participating Pharmacology faculty members include Drs. Beavo, Catterall, Chavkin, Dorsa, McKnight, Nathanson and Storm.

Research Programs and Opportunities

In its research programs, pharmacology is also a bridging discipline. It bridges biochemistry and molecular biology to more integrated systems physiology and pharmacology through its focus on the cellular and molecular mechanisms of signal transduction. This central position in the biomedical sciences provides unparalleled opportunities for interesting research in pharmacology as well as at the interfaces of pharmacology with these related disciplines. The department has focussed on several interlocking research themes: Molecular Pharmacology and Cellular Regulation, Molecular Neurobiology and Neuropharmacology, Cardiovascular Signal Transduction, and Molecular Toxicology. Research activities in each of these areas by the primary and joint faculty members are briefly summarized below. These research programs are

amplified by those of the adjunct faculty, but most of the adjunct faculty research programs are not described here to conserve space. However, it is important to note that the adjunct faculty members are members of our Graduate Faculty in Pharmacology and are eligible to chair Ph.D. committees. The list of the names and research areas of our adjunct faculty members is given in *Appendix F*.

Molecular Pharmacology and Cellular Regulation

The Department of Pharmacology is a leading center for research on cellular signal transduction. The goal of research in this area is to understand the fundamental processes that cells use to regulate their function and relate them to the mechanisms of action of hormones and drugs. One important focus is the cAMP second messenger pathway, a primary target for cellular regulation by hormones and drugs. Professor Emeritus Edwin Krebs led the department in this direction with his pioneering research on cAMP-dependent protein kinase and its role as a widespread effector of hormonal regulation mediated by cAMP. Currently, Dr. Stan McKnight studies the function of the cAMP-dependent protein kinase using mouse genetic methods. By deleting genes encoding specific kinase subunits, he has defined the physiological roles of specific regulatory and catalytic subunits in energy metabolism in brown adipose tissue, regulation of development in the heart, and synaptic plasticity in the brain. Dr. Daniel Storm studies adenylyl cyclase, the enzyme that synthesizes cAMP. Over many years, he and his colleagues have defined the molecular components of the calcium/calmodulin-regulated isoforms of adenylyl cyclase and probed their regulation by protein phosphorylation and by binding of calcium and calmodulin. Dr. Joseph Beavo's research focusses on cyclic nucleotide phosphodiesterases, the enzymes that hydrolyze cyclic AMP and cyclic GMP and thereby terminate their action as second messengers. His work has defined eleven distinct families of phosphodiesterases and characterized their modes of regulation, their specificity for hydrolysis of cyclic nucleotides, and their response to specific drugs. His work has shown that regulation of cyclic nucleotide signaling pathways depends equally on regulation of the synthesis of the messenger molecules by cyclase enzymes and on degradation of the messenger molecules by phosphodiesterases. Dr. Rejean Idzerda studies the protein inhibitor of cAMP-dependent protein kinase, PKI. This protein serves to inhibit the activity of cAMP-dependent protein kinase and to mediate its transport out of the nucleus of cells. Using gene knock-out methods, Dr. Idzerda has shown that deletion of PKI significantly alters gene regulation in skeletal muscle, implicating this protein as an additional point of regulation of cAMP signal transduction in vivo.

Dr. Randall Moon studies an entirely different signal transduction cascade—the *wnt* signaling pathway that guides many of the morphogenetic events in development. His work has shown

that localized expression of specific *wnt* genes is essential for normal formation of the neural tube and neural plate and for determination of dorsal-ventral polarity in development. He has also defined novel downstream signaling events in the *wnt* pathway, including identification of the frizzled receptors for the *wnts*, demonstration of *wnt*-induced migration of β-catenin during morphogenesis, and discovery of a protein kinase C-based signalling pathway initiated by *wnts*. The regulatory events defined in his work are crucial in normal development and control of cellular growth and differentiation and are often altered in developmental abnormalities and in cancer.

Dr. Edith Wang studies the control of cell proliferation at the molecular level, a central problem in cell biology and cancer biology. Tumors arise from cells that are no longer under normal proliferative control, often due to mutations caused by endogenous or environmental factors. Better understanding of the signaling pathways controlling cell proliferation will be important for the development of new approaches to cancer chemotherapy. The intimate link between the regulation of gene expression and cell cycle control has been further strengthened by Dr. Wang's discovery that the $TAF_{II}250$ subunit of the transcription factor IID is identical to CCG1 (cell cycle gene 1), a gene able to suppress the late G_1 arrest observed in the temperature-sensitive mutant hamster cell line ts13. A single amino acid change in $TAF_{II}250$ is responsible for the mutant cell cycle phenotype, and this mutation affects transcription from only a select subset of genes. Dr. Wang has observed that transcription from the promoters of the genes encoding the G_1 cyclins A, D1, and E, but not c-fos and c-myc, is reduced in ts13 cells. However, the exogenous expression of the three G_1 cyclins in ts13 cells does not overcome the cell cycle arrest, suggesting the presence of additional $TAF_{II}250$-dependent genes involved in the ts13 proliferative defect. Dr. Wang is currently using this as an assay to discover novel cell-cycle-dependent factors that are required for normal control of proliferation. She is also characterizing the histone acetyltransferase activity and core promoter function(s) of the wild-type and mutant proteins to determine whether these activities are involved in defining the promoter specificity of the ts13 transcriptional defect. Her long-term goal is to reveal novel regulatory pathways involved in the control of cell cycle progression and its alteration by mutations that lead to uncontrolled cell growth and cancer.

Molecular Neurobiology and Neuropharmacology

Learning, remembering, controlling our emotions, and sensing and responding to our environment all involve the generation and transmission of electrical and chemical signals in the brain. Pharmacological agents that alter these processes are central to the therapy of neurological and psychiatric disease. Revolutionary advances are taking place in our

understanding of the signaling molecules of the brain, their role in brain function, and their significance as targets for drug therapy and drug abuse. The faculty of the Department of Pharmacology study a wide range of neuronal signal transduction processes. Dr. Charles Chavkin studies the opiate receptors that respond to endogenous opioid peptides and exogenous opiate drugs like morphine and heroin. His laboratory has shown that the opiate peptides are endogenous neurotransmitters and neuromodulators in the hippocampus where they regulate the efficacy of synaptic transmission at both excitatory and inhibitory synapses. Release of the opiate peptide dynorphin onto synapses in the dentate gyrus inhibits long-term potentiation, a cellular correlate of learning and memory, implicating the endogenous opiate system in memory formation. His experiments also show that many of the effects of the opioid peptides are mediated by regulation of the activity of potassium channels in neurons, both by indirect pathways involving second messengers and by direct coupling to the G proteins activated by receptor occupancy. These results connect the opiate receptors to cellular signaling pathways used by many other neurotransmitters, potentially permitting the actions of these elusive agents to be understood in detail. This research is of special importance in understanding the tolerance, dependence, and addiction induced by abuse of opiate drugs, a problem of immense importance to society and to biomedical science.

Dr. Neil Nathanson studies two different families of receptors that are important for neuronal function. The muscarinic acetylcholine receptors regulate neuronal firing in many different brain regions. Dr. Nathanson's work has characterized the regulatory pathways that control down-regulation of these receptors by their agonist acetylcholine and related agents. Recent work defines specific amino acid sequences in different muscarinic receptor subtypes that control their specific patterns of down-regulation. Dr. Nathanson has used gene knock-out methods to probe the physiological and pharmacological roles of individual muscarinic receptor subtypes. Using this approach, the m1 receptor was shown to be crucial for the epileptogenic effects of pilocarpine in brain and the m1 and m2 receptors were shown to couple specifically to different forms of calcium channel regulation. Dr. Nathanson also studies the receptors for the cytokine family of neuropeptide regulators. These receptors regulate neuronal development and cell-cell interactions by activating intracellular signaling through the MAP kinase pathway and other phosphorylation cascades.

Dr. Daniel Dorsa, a joint faculty member with Psychiatry & Behavioral Sciences, studies the effects of estrogen on brain function and neuropharmacology. Estrogen receptors in the brain mediate acute effects of these hormones on excitability, synaptic transmission, and behavior, as well as regulating gene expression as observed in other tissues. Dr. Dorsa's work provides

evidence for neuroprotection by estrogens against the adverse effects of cellular stress and the effects of neurodegenerative diseases. Dr. Nephi Stella, our second joint faculty member with Psychiatry & Behavioral Sciences, has just begun to establish his research program on lipid signaling systems in neurons, focussing on cannabinoid receptors and their endogenous ligands. His research area will broaden the department's expertise to include lipid signaling pathways in neurons and other cell types and will further extend our work on the mechanisms of action of drugs of abuse.

Dr. Joseph Beavo and Dr. Daniel Storm study the cAMP and calcium regulatory pathways that transduce the signals from many neurotransmitter receptors in neurons. Dr. Storm and his colleagues have shown that calcium/calmodulin-regulated adenylyl cyclase is highly expressed in regions implicated in learning and memory such as the hippocampus. Studies with knock-out and transgenic mice show that this enzyme is essential for normal long-term potentiation in the hippocampus and for spatial learning in response to environmental cues. Moreover, activation of this enzyme is required for increased gene expression associated with the late phase of long-term potentiation of synaptic transmission. This increase in calcium- and cAMP-driven gene expression is observed in response to learning paradigms, suggesting that it is an essential component of the neuronal adaptations that underlie learning and memory. Dr. Beavo and his colleagues study the cyclic nucleotide phosphodiesterases, which degrade cAMP amd cGMP in neurons. Their research has been instrumental in identifying neuro-specific isoforms that are highly expressed in the specialized sensory neurons of the visual system (the rods and cones) and the olfactory system (the olfactory epithelial neurons) and have been implicated in the cyclic nucleotide signal transduction cascades that are activated by visual and olfactory stimuli.

Research in the laboratory of Dr. Sandra Bajjalieh focuses on the molecular mechanisms of synaptic transmission. In the presynaptic terminal, a cascade of protein-protein interactions is involved in movement of synaptic vesicles to the presynaptic plasma membrane, docking at active zones, sensing incoming calcium from a nerve impulse, triggering vesicle exocytosis, and finally recovering the vesicle membrane and synthesizing a new vesicle. Dr. Bajjalieh has cloned and defined the primary structure of synaptic vesicle protein 2 (SV2), a ubiquitous component of synaptic vesicles with a complex, twelve-membrane-spanning structure whose function is unknown. She has also discovered a novel ceramide kinase associated with synaptic vesicles. She is now studying the functional roles of these two proteins in the mechanism and regulation of neurotransmitter release. Biochemical studies show that the SV2 protein interacts directly with synaptotagmin, the putative calcium sensor for neurotransmitter release. Targeted disruption of the SV2 genes yields mice with epilepsy and defects in inhibitory GABAergic

neurotransmission. These knock-out mouse models now provide an exciting approach to analysis of SV2 function in synaptic transmission. Possibilities include regulation of vesicle function by acting as a transporter of a crucial vesicle component or catalysis of exocytosis as a component of the fusion pore that initiates membrane fusion.

Dr. William A. Catterall and Dr. Todd Scheuer study the sodium and calcium channels that are responsible for electrical excitability of neurons. Previous work in the Catterall lab led to the discovery of the protein components of sodium and calcium channels, determination of the complex multi-subunit structures of these channels, and reconstitution of their ion conductance activity from purified components. Current work in the Catterall and Scheuer labs focuses on the structure and function of these ion channel proteins and their regulation and physiological function in neurons. Analysis of the molecular mechanism of sodium channel inactivation has identified the inactivation gate of the sodium channel and defined its function as an intracellular hinged lid that closes the channel after opening. Studies of sodium channel regulation have shown that they are modulated by multiple second messenger pathways including phosphorylation by both cAMP-dependent protein kinase and protein kinase C and direct binding of G protein $\beta\gamma$ subunits. Calcium channels in presynaptic nerve terminals are responsible for the calcium entry that initiates transmitter release. Recent work in the Catterall and Scheuer labs has shown that these channels are also modulated by direct binding of G protein $\beta\gamma$ subunits. Moreover, the presynaptic calcium channels interact directly with the SNARE proteins that are involved in docking and release of synaptic vesicles at synapses, and this interaction is also modulated by protein phosphorylation. Experiments in progress aim at understanding how the interactive processes of inactivation, modulation by protein phosphorylation, and modulation by G proteins work together to control neuronal excitability and synaptic function.

Dr. Bruce Tempel studies the potassium channels that are responsible for setting resting membrane potential and controlling electrical excitability of neurons and other cell types. As a postdoctoral fellow, he cloned the first potassium channel genes from Drosophila and vertebrates. His laboratory now studies the physiological role of potassium channels, with emphasis on their role in the auditory system. His work has shown that potassium channels form specific hetero-oligomers with specific subcellular localizations in neurons and that deletion of specific potassium channel genes results in epilepsy and other disorders of hyperexcitability.

Cardiovascular Signal Transduction and Pharmacology

Current research has shown that many of the cellular signaling pathways that are used in the brain to process information and to control physiological function are important in other cellular

systems including the heart and vasculature. Research in this area is supported by a Program Project Grant on Molecular Mechanisms of Signal Transduction in the Heart as well as by multiple individual research grants. The work focuses on the physiological and pharmacological regulation of sodium and calcium channels in cardiac excitability and the regulation of the heart and vasculature by the cAMP and cGMP signal transduction cascades.

Research by Drs. Catterall and Scheuer has defined the receptor sites for drugs that block sodium and calcium channels in the heart. Local anesthetics and local anesthetic-like antiarrhythmic drugs have been shown to interact with a receptor site in the sixth transmembrane segment in homologous domain IV of the sodium channel α subunit (segment IVS6). Although traditional local anesthetics have different structural features than most antiarrhythmic drugs, all these different drugs interact to differing degrees with the same amino acid residues in the local anesthetic receptor site. Similarly, calcium channel blockers have been shown bind to three distinct but interactive receptor sites in domains III and IV of the calcium channel $\alpha 1$ subunit. Their receptor sites involve amino acid residues in transmembrane segments IIIS5, IIIS6, and IVS6. Proof of this localization of the receptor site for the dihydropyridine class of calcium channel blockers has come from complete construction of a minimum dihydropyridine receptor site in a drug-insensitive neuronal calcium channel by substitution of only 9 of over 2000 amino acid residues in the subunit. This work is an important advance in understanding of the molecular mechanism of action of these widely used therapeutic agents.

Dr. Nathanson's laboratory studies the regulation of the muscarinic acetylcholine receptors in the heart. The m2 receptor is the primary isoform expressed in the heart. Its inhibition of adenylyl cyclase and activation of the inward rectifying potassium channels are important regulators of beat rate and cardiac contractility. Recent research has shown that down regulation of this receptor involves both a G protein-coupled receptor kinase and arrestin as intracellular effectors. In addition, Dr. Nathanson has collaborated with Dr. Eric Feigl to show that targeted deletion of the m1 muscarinic receptor gene reduces both the inotropic and chromotropic effects of subtype-specific muscarinic agonists like McN A-343, suggesting that the m1 receptor has an important role in regulation of cardiac contractility and beat rate, in addition to the well-documented effects of m2 receptors.

The regulation of cardiac function by the autonomic nervous system depends critically on the cAMP pathway. Activation of β-adrenergic receptors by epinephrine or norepinephrine activates adenylate cyclase, increases cAMP, activates cAMP-dependent protein kinase, and regulates sodium and calcium channels by protein phosphorylation. This regulation is turned off by

hydrolysis of cAMP by cyclic nucleotide phosphodiesterases. Each step in this essential regulatory pathway is studied by faculty members of this department. Dr. Storm studies activation of adenylate cyclase by receptors and G proteins. His group has identified a novel adenylate cyclase isoform in the heart, which is regulated by calcium and calmodulin and therefore is a point of intersection of the cAMP and calcium signaling pathways. Dr. McKnight studies the cAMP-dependent protein kinase. His group has produced and analyzed mice with targeted deficiencies in each of the regulatory and catalytic subunits of this enzyme. Analysis of the changes in cardiac regulation in these mice has revealed which kinase subunits are essential for cardiac development and physiological regulation and has suggested that both the type I and type II regulatory subunits can be anchored by A Kinase Anchoring Proteins (AKAPs) near their target substrates. Drs. Catterall and Scheuer have analyzed the regulation of cardiac sodium and calcium channels by the cAMP pathway. Sites of phosphorylation that are responsible for channel regulation have been identified and the interaction between phosphorylation and membrane depolarization in regulation of channel function has been defined. Dr. Beavo's group has demonstrated that specific isoforms of the cyclic nucleotide phjosphodiesterases are important for termination of the regulatory actions of cAMP in the heart. Agents which target these isozymes are effective positive inotropic agents and are potential therapeutic agents in treatment of congestive heart failure. Altogether, the work on cardiac signal transduction has yielded critical new insights into the function and regulation of the heart.

Molecular Toxicology

Drugs and environmental chemicals have toxic effects that cause short term illness and have long-term negative impacts on health and well-being. Rational design of drugs which lack toxic side effects and recognition of the hazardous chemicals in the environment require an understanding of the mechanisms of toxicity of these agents in developing and adult organisms. Research in the Department of Pharmacology focuses on effects of environmental chemicals on organogenesis and early development, the effects of mutations on control of cell growth and development of cancer, and the effects of drugs and environmental toxins on neuronal function and cell death.

Dr. Mont Juchau and his colleagues study the effects of environmental chemicals on early development of mammalian embryos and the changes in the drug-metabolizing enzymes of the cytochrome P450 family that are responsible for biotransformation of these agents. Their recent research has established that the retinoid family of cellular signaling molecules can act as direct teratogens, inducing dysmorphogenesis of multiple developing organs. Local metabolism of the retinoids controls their actions as dysmorphogens as well as their normal physiological role as

developmental regulators. Similarly, other xenobiotic compounds such as benzene and its metabolites, polycyclic aromatic hydrocarbons produced in tobacco smoke, and acetylaminofluorene also act as teratogens and dysmorphogens depending on their local metabolism by enzymes of the P450 family. Dr. Juchau and his colleagues are now pursuing an important new direction in their research, based on the finding that developing human brain expresses a surprisingly broad array of P450 enzymes which may be critical factors in metabolism of xenobiotic compounds in the human embryo. Dr. Frank Vincenzi and Dr. Thomas Hinds study the cytoxic effects of oxygen free radicals, which are produced in tobacco smoke, during xenobiotic metabolism, and in the course of normal cellular function. Their work shows that calcium ATPases are sensitive targets for inhibition by oxygen free radicals, providing a cellular mechanism through which free radicals and elevated intracellular calcium may work synergistically to damage cells.

As described above under Molecular Pharmacology and Cellular Regulation, Dr. Edith Wang studies the mechanisms of action of mutations that alter cell growth and regulation. Her work shows that these mutations alter growth control by altering gene expression, including expression of the cyclin genes. In addition, Dr. Curt Omiecinski, an adjunct faculty member in the Department of Environmental Health of the School of Public Health and Community Medicine, studies the regulation of expression of the genes encoding drug metabolizing enzymes containing cytochrome P450 by drugs and other environmental factors. His research uses a novel liver tissue culture preparation that retains responsiveness of gene regulation in vitro, allowing incisive analysis of the mechanisms of control of gene expression. He has recently been able to reconstitute phenobarbital responsiveness of expression of the cytochrome CYP2B2 gene in transgenic mice expressing 2.5 kb of 5'-flanking DNA, providing another incisive tool for analysis of the molecular basis for regulation of drug metabolism.

Dr. Daniel Storm and his colleagues are studying an unexpected form of neurotoxicity. They have shown that the active ingredient in marijuana, Δ9-tetrahydrocannabinol, is toxic to neurons in hippocampal slices in vitro. The affected neurons undergo cell death that has some of the features of apoptosis. This work may give insight into the memory loss and other psychological side effects that accompany chronic marijuana use in humans.

Analysis of the molecular mechanisms of biological and environmental toxins that act on voltage-gated sodium channels is a longstanding interest of Dr. Catterall. Sodium channels are the molecular targets of a wide array of paralytic toxins produced by scorpions, frogs, salamanders, fish, plants, and marine dinoflaggelates in plankton. All of these toxins are

significant biological hazards, and the saxitoxins, brevetoxins, and ciguatoxins produced by marine dinoflaggelates are important environmental toxins which affect fish and shellfish supplies in the Pacific Northwest and many other coastal areas. Early work showed that these diverse toxins act on a set of at least five distinct receptor sites on sodium channels. Present research is directed at identification of these receptor sites at the molecular level on the sodium channel protein. So far, the receptor sites for scorpion toxins have been defined at the single amino acid level, and the receptor sites for brevetoxins, ciguatoxins, and the poison frog toxin batrachotoxin have been traced to one or two specific transmembrane segments of the 24 membrane-spanning sequences in the complex sodium channel molecule. Future work in this area will result in a detailed understanding of the molecular basis for the toxic effects of this broad class of highly toxic agents.

C. Department and University View of Departmental Functions

The views of the academic goals of the department from the university and departmental perspectives are congruent. Thus, both the faculty of the department and the administration of the University and School of Medicine expect excellence in teaching, research, and research training combined with participation in the academic leadership of the School of Medicine and the University. As described above, the Department of Pharmacology has taken advantage of these opportunities by developing outstanding research and educational programs in pharmacology and by participating actively in interdisciplinary programs related to pharmacology. The close, synergistic relationship of the research and educational activities of the department is a strength that we hope to continue in future departmental development.

D. Changes in Discipline and in Departmental Role

In the past ten years, major changes have taken place in research and graduate education in pharmacology, as in most of the disciplines of the biomedical sciences. We highlight three major trends here—the strong development of interdisciplinary graduate training programs at UW and elsewhere, the increasing impact of computer-based technologies in education and research, and the impact of cellular, molecular, genetic, and structural approaches to studies of pharmacology and cellular regulation. The Department's steps to address each of these challenges are described below.

Impact of interdisciplinary graduate training. During the past ten years, the number, diversity, and quality of interdisciplinary graduate programs have greatly increased, and these programs

have flourished. This is a very welcome and important development in graduate education in the biomedical sciences, allowing students a much richer set of choices for graduate education and providing educational opportunities in broad areas not easily covered in departmental programs. Faculty members in the Department of Pharmacology have been instrumental in developing two of the interdisciplinary graduate programs at UW. The Graduate Program in Neurobiology was founded by Dr. William Catterall, who served as its first Director, and it has been led for the past ten years by Dr. Neil Nathanson, Professor of Pharmacology. In 1995, the program merged with the Physiology/Psychology Graduate Program to form the present Graduate Program in Neurobiology & Behavior. This program has been very successful in establishing an excellent integrated curriculum on neurobiology and behavior and in attracting and training outstanding graduate students. The Molecular and Cellular Biology Program was begun by a consortium of ten basic biomedical science departments in the School of Medicine and the College of Arts & Sciences approximately ten years ago. It expanded to include the faculty at the Fred Hutchinson Cancer Research Center as well as additional faculty at UW. For the past several years, it has been directed by Dr. Randall Moon, Professor of Pharmacology.

Although the faculty members of the Department of Pharmacology participate actively in these two large interdisciplinary graduate programs, they are equally committed to sustaining and enhancing the quality of the Graduate Program in Pharmacology. The Graduate Program in Pharmacology is distinct from the interdisciplinary programs in its clear focus on pharmacology and signal transduction as primary research areas as well as in its curriculum, which includes intensive course work in pharmacology and physiology in addition to the cell and molecular biology courses taken by all graduate students. Students attracted to this graduate program have already made a decision that pharmacology and cellular signal transduction are their major interest areas and have sought out a graduate program focussed on these subjects. Thus, the Graduate Program in Pharmacology serves a distinct student population from the interdisciplinary graduate programs and thereby complements the larger multi-departmental programs in both training focus and in student group. It is the goal of the faculty in the Department of Pharmacology to enhance the quality of our graduate program and improve the focus on its areas of strength in order to serve this distinct student group better and to train the leaders in pharmacology for the future. Toward this end, we maintain an active student recruitment program and provide fellowship support for the students through departmental and university resources and through training grants. We have also expanded the research and training expertise of our faculty by appointment of joint and adjunct faculty members whose research represents emerging areas of biomedical science relevant to pharmacology. In the past decade, new adjunct faculty members have been added to the department in the areas of

neurodegenerative disease (Dr. Gerald Schellenberg and Dr. David Cook), neuropharmacology of serotonin receptors (Dr. Mark Hamblin), signal transduction in the visual system (Dr. Krzysztof Palczewski), and regulation of gene expression by intracellular signaling pathways (Dr. Karol Bomsztyk). These new adjunct faculty substantially expand the research training opportunities for graduate students.

Increase in computer–based research and education. As in all areas of modern life, use of computers in research and education has dramatically increased in the past decade. Easy access to computers for word processing, data analysis, and graphics is essential for graduate students, but their personal budgets often do not allow purchase of up-to-date equipment. To address this problem, the Department of Pharmacology has developed a graduate student computer laboratory with the help of a grant from the Student Technology Fee Fund of the University of Washington. This facility provides six computer work stations that are connected through ethernet to all of the university's computing resources as well as departmental printers and data analysis equipment. This facility has been very helpful to graduate students to introduce them to current computer technology and provide access for easy use for word processing, data analysis, graphics and bioinformatics.

New experimental approaches in pharmacology. Over the past twenty years, research in pharmacology has been transformed by the application of biochemical, cellular, and molecular biological methods to traditional problems of drug action, receptor function, and cellular regulation. This department was a leader in incorporating these rapidly evolving experimental approaches into its research programs during the late 1970's and the 1980's. In the past decade, genetic methods have had a similarly profound impact. Mouse genetics has allowed the use of gene knock-out technology to probe the function of receptors, kinases, ion channels, and other signaling molecules in an *in vivo* context. Genomic sequencing has provided the molecular templates for analysis of most of the genes in higher organisms. These developments have provided unparalleled new opportunities for research in pharmacology.

The Department of Pharmacology has responded to these new opportunities by aggressively incorporating these new experimental approaches into its research programs. Beginning with the founding of the Molecular Pharmacology Facility, the W. M. Keck Center for Research in Neural Signaling, and the Program Project in Molecular Mechanisms of Cardiac Signal Transduction approximately ten years ago, a centralized effort was made to facilitate introduction of molecular biological methods and mouse genetic methods into standard research practice in the department. The Molecular Pharmacology Facility provides equipment and

expertise for protein sequencing, peptide synthesis, automated DNA sequencing, and oligonucleotide synthesis. Both the Keck Center and the Program Project provide support for molecular biology and mouse genetic research. The Keck Center also provides high resolution confocal microscopy and calcium imaging technology for use in departmental research programs. These efforts, and collaborative interactions among the labs in the department, allowed faculty members to quickly establish these new methods in their laboratories. At present, every lab in the department uses molecular biology methods effectively as an integral part of its research program, and many labs use confocal microscopy and calcium imaging. Moreover, following the lead of Drs. Stan McKnight, Rejean Idzerda, and Dan Storm, more than half of the faculty members have incorporated mouse genetic methods into their research, and this work has led to a long list of important papers in leading journals. We hope to use similar approaches to respond to emerging experimental technologies in the coming decade, as described in Section IV below.

E. Criteria for Assessment of the Quality of Departmental Programs

The Department of Pharmacology uses several criteria to assess the quality of its research and education programs with respect to national and international standards and with respect to local university requirements. Additional criteria are used to evaluate the standing of the Graduate Program in Pharmacology, as outlined in Section III (page 28).

Research funding. The total level of research funding and the research funding per primary faculty member provide an assessment of the scope and quality of faculty research programs through the eyes of national review committees.

Citation number and frequency. Citation of research articles by other peer investigators is an important means of assessing the impact of the research of the faculty.

National committees and service. Service of faculty on editorial boards, review panels, and national committees are also important indicators of an active faculty whose expertise is recognized on a national and international level.

University administrative responsibilities. Service of faculty members as leaders of educational and research programs at UW provides an indication of recognition by their faculty peers of their academic qualities and their personal leadership capabilities.

Student and faculty reviews of teaching. Reviews of teaching effectiveness by faculty and students are an important means of assessment of educational quality.

Honors and awards. Recognition of faculty research by receipt of honors and awards from professional societies and other national bodies is a valuable indicator of the quality of the research and academic programs in which the faculty members participate since the success recognized by such awards requires not only individual excellence but also an excellent programmatic infrastructure for research and teaching.

F. Quality of Departmental Research and Educational Programs

Based on the criteria outlined above, the research and educational programs of the Department of Pharmacology are highly successful. The total research funding of the department (approximately $7.9M per year) is consistently ranked in the top five pharmacology departments nationally. In rankings by the National Institutes of Health of departments receiving NIH research grants, the Department of Pharmacology also consistently ranks in the top six. Similarly, in rankings by the Association for Medical School Pharmacology, the society of pharmacology chairs, the Department of Pharmacology also ranks among the top five departments in total research funding. Because we are smaller than average for pharmacology departments, with only 13 primary faculty members, our research funding per primary faculty member is in the top two or three nationally.

The faculty members of the Department of Pharmacology are very active in publication of their research findings. As illustrated on page 23, in *Table 1. Publication and Citations*, the primary and joint faculty averaged 5 to 6 total research publications per year per faculty member for the past decade. These papers have been widely cited. Papers published through 1996, whose total citations are nearing maximum, have been cited an average of 31 to 74 times. There have been fewer total citations of more recent papers because there have been fewer years in which to cite them. Overall, the Department of Pharmacology has a strong publication record, consistent with its strong record of research funding and research.

Table 1. Publications and Citations

Year	Primary and Joint Faculty	Total Publications	Publications per Faculty Member	Citations per Faculty Member	Citations per Paper
1990	14	71	5.1	376	74
1991	14	78	5.6	342	61
1992	14	88	6.3	320	51
1993	14	84	6.0	236	39
1994	14	80	5.7	220	39
1995	16	111	6.9	334	48
1996	16	80	5.0	156	31
1997	16	100	6.3	104	17
1998	17	87	5.1	42	8.2
1999	17	75	4.4		

The faculty members of the Department of Pharmacology are very active in service on editorial boards, review panels, and national committees. All of the senior faculty members have major responsibilities of this kind. The list of such memberships is too long to present here, but the current editorial, review, and committee responsibilities of the faculty are indicated in their brief curricula vitae, which are included in *Appendix F*. The faculty members of the department also have received numerous honors and awards for their research activities. Three faculty members are members of the National Academy of Sciences and one is a Nobel Laureate.

The faculty members of the Department of Pharmacology are often called upon to serve in administrative capacities within the University of Washington. Current examples include service of Dr. Daniel Dorsa (Professor of Psychiatry & Behavioral Sciences and Pharmacology) as Associate Dean for Graduate Education and Research; Dr. Neil Nathanson (Professor of Pharmacology) as Director of the Graduate Program in Neurobiology & Behavior; Dr. Randall Moon (Professor of Pharmacology and Investigator of the Howard Hughes Medical Institute) as Director of the Molecular and Cellular Biology Program; Dr. Charles Chavkin (Professor of Pharmacology) as Associate Director of the Alcohol and Drug Abuse Institute; Dr. William Catterall (Professor and Chair of Pharmacology) as Chair of the Interdisciplinary Committee on Neurobiology; Dr. Stanley McKnight (Professor of Pharmacology) as a member of the Appointment and Promotions Committee of the School of Medicine; Dr. Frank Vincenzi (Professor of Pharmacology) as a member of the Academic Affairs Committee of the School of

Medicine; and Dr. Lawrence Halpern (Professor of Pharmacology) as a member of the Curriculum Committee and the Admissions Committee of the School of Dentistry.

Reviews of the teaching and research training program of the Department of Pharmacology by health science professional students and by graduate students have been consistently good. Similarly, the work of our graduate students as teaching assistants is consistently rated highly by their student groups. Thus, the educational programs of the department are successful and appreciated by their constituencies.

G. Collaborations with Other Institutions

We have just begun a series of research exchanges with the Vollum Institute in Portland, OR. The Vollum Institute has built an outstanding research program with similar emphases as this department on molecular pharmacology, cellular regulation, and neurobiology. The first joint meeting in September, 1999, organized by Dr. Tom Soderling at the Vollum Institute and Dr. Stan McKnight of our department, was very successful and we anticipate that this joint meeting will enrich both faculties for years to come.

Collaborative research programs between individual laboratories in our department with investigators at other universities are very common. Virtually every faculty member in our department with an active research program has published at least one paper with collaborators from other institutions.

H. Collaborations with Departments at University of Washington

The Department of Pharmacology has both educational and research collaborations with colleagues at the University of Washington. Educational collaborations have been described above. They include NIH-funded research training programs in Pharmacological Sciences, Molecular and Cellular Biology, Neuroscience, Molecular Neurobiology, Molecular Mechanisms of Drug Abuse, Cardiovascular Pathology, and Environmental Pathology as well as UW interdisciplinary programs in Molecular and Cellular Biology and Neurobiology & Behavior.

The W. M. Keck Center for Research in Neural Signaling is a collaborative research program of the Department of Pharmacology and the Department of Physiology & Biophysics. Originally funded by a grant from the W. M. Keck Foundation, the Keck Center has catalyzed joint research

programs, faculty research development, and a joint Imaging Facility with equipment for confocal microscopy and calcium imaging.

Faculty members in the Department of Pharmacology have many collaborative research programs with other faculty at UW. Interactions are most well developed with the Department of Physiology & Biophysics, the Department of Biochemistry, and the Department of Psychiatry & Behavioral Sciences. A few examples suffice to illustrate the extent of these interactions. Dr. Eric Feigl of the Department of Physiology & Biophysics serves as Director of the Cardiac Physiology Core of our Program Project on Molecular Mechanisms of Cardiac Signal Transduction. Publications with Drs. Neil Nathanson and Stan McKnight have resulted from this work. Dr. William Catterall, Dr. Neil Nathanson, and Dr. Bruce Tempel have all collaborated with Dr. Bertil Hille of the Department of Physiology & Biophysics on projects focussed on regulation of potassium and calcium channels. Dr. Catterall and Dr. Rachel Klevit of the Department of Biochemistry and Biomolecular Structure Center have worked together to define the three-dimensional structure of the sodium channel inactivation gate. Dr. Catterall and Dr. Joe Beavo have collaborated with Dr. Kenneth Walsh of the Department of Biochemistry on determination of the primary structures of ion channel subunits and phosphodiesterase isozymes. Dr. Beavo and Dr. Wim Hol of the Department of Biological Structure are working together on the structure of cyclic nucleotide phosphodiesterases. Dr. Charles Chavkin and Dr. Stan McKnight have collaborated with Dr. Dan Dorsa and others in the Department of Psychiatry & Behavioral Sciences on the behavioral effects of deletion of receptor and protein kinase genes in mice. Dr. Dan Storm and Dr. Stan McKnight have collaborated with Dr. Richard Palmiter of the Department of Biochemistry on studies of mice deficient in specific adenylyl cyclase and protein kinase isoforms. Dr. Randall Moon and Dr. David Raible of the Department of Biological Structure have collaborated on studies of *wnt* genes in zebrafish development. As these examples illustrate, there is an extensive network of collaborations among faculty members in the Department of Pharmacology and other departments at UW.

III. Degree Programs

Graduate Degree Programs: Master of Science and Doctor of Philosophy Degrees

The Department of Pharmacology offers programs leading to the Master of Science and Doctor of Philosophy degrees. Graduate students are accepted as Ph.D. students; terminal Master's

degree students are not accepted. The Master of Science degree may be elected by the student or requested by the department.

Entrance Requirements

Each year, six or seven new students are accepted in the Ph.D. program. The students are selected from the applicant pool based on several criteria: academic records, standardized test scores (i.e., Graduate Record Examination), recommendations and previous research experience. The Departmental Graduate Admissions Committee evaluates each application on its merits and scores on the Graduate Record Exam and recommends to the faculty as a whole the admission of each student. *Table 2. Average Scores of Entering Class 1990 – 1999* summarizes the average GPA and GRE scores of our entering classes.

Table 2. Average Scores of Entering Class 1990 – 1999

Year	GPA	GRE Verbal	GRE Quant	GRE Analyt	GRE combined
1999	3.49	558	752	723	2033
1998	3.52	535	655	635	1825
1997	3.35	583	697	684	1964
1996	3.42	650	706	726	2082
1995	3.31	615	695	668	1978
1994	3.40	578	670	698	1946
1993	3.62	635	663	687	1985
1992	3.38	591	634	610	1835
1991	3.52	554	716	606	1876
1990	3.63	579	695	624	1898

There are no specific course requirements for admission to the graduate program in Pharmacology. Applicants generally have strong course work in the chemical and biological sciences. Most applicants have a Bachelor's degree in chemistry, biology, biochemistry or pharmacy.

Considerable attention is paid to the quality of the applicant's undergraduate institution, the letters of recommendation, research experience, the applicant's written statement of interest, and potentially relevant employment experiences. The Department of Pharmacology pays for travel expenses for those students that are selected as the primary candidates, and interviews with faculty members provide the final evaluation of each individual.

Curriculum

Master of Science

Program Requirements. The Master of Science degree in Pharmacology is used as a degree alternative for students originally admitted to the Ph.D. program who have performed adequately, but have decided on a different career path or have been judged as unlikely candidates for continuation toward the Ph.D. degree. Acquisition of the M.S. degree is not a requirement for proceeding to the doctorate. The Master's degree program in Pharmacology is a thesis program with the same basic credit requirements as the Graduate School. A minimum of 36 credits must be presented, including nine credits of Master's thesis. As with the Graduate School requirements, a maximum of nine credits of thesis may be used towards the degree. The department requires completion of the Pharmacology series 511, 512, 513, and three additional 500-level pharmacology courses. The student must demonstrate competence in pharmacology and a related discipline, such as biochemistry or physiology, and must present and defend a Master's thesis. A grade of 3.0 or higher must be achieved in required courses for the degree.

Doctor of Philosophy

Program Requirements. The Doctoral Degree in Pharmacology has a single pathway of requirements prior to completion of the general examination, with minor exceptions for students in concomitant degree programs (e.g., M.D./Ph.D. programs).

Typical Course of Studies. In the first year, students generally are expected to enroll in pharmacology, physiology and molecular and cellular biology courses. For each of the academic quarters of the first year, a student may work with a different faculty member. The purpose of rotating among the faculty is to acquaint the student with various areas of pharmacology and research under investigation within the department. With this insight, the student should be better able to decide on a thesis or dissertation topic. In the second year, while becoming more involved with research, the student continues attending courses in pharmacology and supporting disciplines. Reference *Appendix C* for program requirements and a brief description of Pharmacology graduate courses offered.

Laboratory Rotations and Choice of Research Supervisor. During each quarter in the first year of graduate study, the student carries out a research project in the laboratory of one of the faculty members. At the end of each quarter the student presents a ten-minute talk on his or her project. The presentation is evaluated by the faculty using the criteria of scientific content, delivery, knowledge of

the subject, and organization of material. Students receive a grade and academic credits for rotation research. The purpose of rotation research with different members of the faculty is to acquaint the student with the various areas of pharmacology and research problems under investigation within the department. At the end of the third rotation (Spring Quarter) the student is expected to decide on an area of pharmacology in which to work for the Summer Quarter and subsequent year, and to choose a faculty sponsor for his or her dissertation research. Most often, the sponsor is one of the faculty members with whom the student has done rotation research. The choice of sponsor is perhaps the most important decision a graduate student makes in his/her graduate career. The choice must be approved by the prospective faculty sponsor and by the Departmental Chair.

Supervisory Committees. During Spring Quarter of the second year, the student (advised by his or her sponsor and the Graduate Affairs Committee) selects a Supervisory Committee. This committee generally consists of members of the Pharmacology faculty most familiar with the area of research in which the student exhibits major interest, as well as representatives from other appropriate departments. The personnel of the committee will be recommended to the Dean of the Graduate School who will officially appoint the Supervisory Committee, including a Graduate School Representative. The committee then guides the student's training program with regard to further course work, research, and the Ph.D. dissertation and conducts the General and Dissertation Examinations.

General Examination. The General Examination is administered in two parts: a written and oral examination, scheduled by the Graduate School at the request of the department. Immediately after Spring Quarter of the second year, the student will be given the written portion of the General Examination. Within three months after having taken the written portion, the student will be given the oral portion of the General Examination. The examination is based in part on an evaluation of the student's proposed research for the dissertation and on the student's knowledge of the major disciplines important to the research. As a result of the examination, the Committee may recommend termination, further work and subsequent reexamination, or approval of the student's performance and candidacy for the Ph.D. degree. After successful completion of the General Exam, the student devotes most of his or her time to thesis research in the third and subsequent years of study.

Annual Review of Progress. Beginning the fourth year (and each subsequent year annually until graduation), each student is reviewed annually by their supervisory committee regarding their dissertation progress. The student is asked to prepare a two page status report, circulate it to their committee, and meet to discuss it by the end of Winter Quarter.

Dissertation. The research project for the Ph.D. dissertation is chosen by the candidate and faculty sponsor and approved by the candidate's Supervisory Committee. The research must represent a worthy and fundamental contribution showing originality in concept and implementation. When the candidate has concluded the research project and prepared a complete copy of the dissertation, the sponsor will obtain approval of the Graduate School and set a date for the Final Examination. It is the candidate's responsibility to see that each member of the committee receives a copy of the dissertation well in advance of the Final Examination. The Final Examination will be concerned principally with the subject matter of the dissertation, but may include the background and origins of the dissertation problem as well as its practical applications and extrapolations. After successfully completing the Final Examination, the candidate presents two copies of the dissertation to the Graduate School office and one to the Department of Pharmacology before the Doctor of Philosophy Degree is granted.

Teaching Participation. During Fall, Winter and Spring Quarters, second-year graduate students lead one discussion section per week in Pharmacology 401, 402 and 403, *General Pharmacology*, for senior undergraduates in the Doctor of Pharmacy program. This experience prepares graduate students for teaching responsibilities after the award of the Ph.D. and provides a good opportunity for consolidation of the student's general pharmacology background.

Criteria for Evaluation of the Graduate Program in Pharmacology

External review and support of training programs. Review of NIH-supported graduate and postgraduate training programs provide key opportunities for assessment of the quality and impact of our research-oriented training programs.

National surveys and rankings of graduate programs. Periodic ranking of graduate programs by the National Research Council, the National Institutes of Health, and other organizations provide an additional external source of assessment of quality.

Success of graduates. Crucial criteria of the success of graduate education programs are the publications of graduate students during their dissertation research and the placement of graduates in excellent positions upon graduation and further development of their careers.

Evaluation of the Graduate Program in Pharmacology

In the rankings of graduate programs in Pharmacology published by the National Research Council in 1994, our department ranked eighth among its peers. Since three of the more highly

ranked Ph.D. programs have been discontinued in the past several years, while our program has continued to grow stronger, it is likely that our Graduate Program in Pharmacology would be ranked more highly today.

Recent reviews of our research training programs by national committees also provide evidence of a high national ranking. In the past year, the Pharmacological Sciences Training Program received a priority score of 145 for renewal of our predoctoral training grant, and the grant was renewed with increased funding. Similarly, in recent competitive reviews, the Molecular Neurobiology Training Program headed by Dr. Catterall received a priority score of 140, the Molecular Mechanisms of Drug Abuse Training Program headed by Dr. Chavkin received a priority score of 136, and the Graduate Neuroscience Training Program, in which several faculty members participate, received a priority score of 173. All of these training grants were renewed with enthusiastic support from the review committees. These very positive reviews by critical national committees indicate that our research training programs are highly successful and nationally recognized.

Our graduate students are highly successful in publishing their research. Our students have averaged 5 publications from their thesis research *(Table 3)*.

Table 3. Student Productivity 1990 - 2000

Year	No. of graduating students	No. of Papers published by graduates	Avg. no. of papers per student
1990	6	31	5
1991	6	38	6
1992	10	48	5
1993	1	6	6
1994	4	24	6
1995	8	41	5
1996	13	64	5
1997	10	38	4
1998	8	39	5
1999	2	6	3
2000	2	13	7

This includes all papers published with their thesis supervisor, whether they appeared during their dissertation research or shortly thereafter.

The graduates of our Master's and Ph.D. programs have also given the department high ratings for its research and educational programs and for providing an opportunity for outstanding research training. These ratings are collected by the Graduate School and are summarized in the *Appendix B*.

Equally important, our graduates at both Master's and Ph.D. levels have been successful in obtaining positions that provide outstanding career opportunities. In *Appendix F, Placement of Graduates of Current Faculty Members*, a complete list of the graduates of our current faculty is presented. From this list, *Table 4* summarizes the career paths of our graduates in several categories. For students entering before 1990, more than 57% have positions in academic institutions or nonprofit research institutes. For students entering between 1980 and 1989, another 33% have positions in the biotechnology industry, reflecting the increase in research activity in biotechnology companies in recent years. For students entering after 1990, there is an increasing trend toward positions in the biotechnology industry, but it is likely that this is skewed because there has not been sufficient time for most students entering after 1990 to complete the long postdoctoral training that is now required to compete for academic positions.

Table 4. Placement of Graduates of Current Faculty Members

	Entering Year		
Career Path	Pre-1980	1980-89	1990-1999
Academic	26 (59%)	25 (51%)	4 (22%)
Nonprofit Research Institute	3 (6.8%)	3 (6.1%)	--
Pharmaceutical	--	2 (4.1%)	3 (17%)
Biotechnology	7 (15.9%)	16 (33%)	5 (28%)
Government/Regulatory	2	--	--
Medical	--	1	3
Pharmacist	1	--	--
Postdoctoral	--	6	15
Unknown or Other	5	2	3
Retired	6	--	--
Deceased	4	2	--
Total	*54*	*57*	*33*
*Total in Career Positions**	*44*	*49*	*18*

*Total in career positions = total – (retired, deceased, postdocs)

% values reflect % of total in career positions

These favorable results in careers attest to both the quality of the students in our graduate program and to the quality of their research training experience at UW.

IV. Expected Changes in Research and Education in Pharmacology

Section IID above describes major changes in research and education in Pharmacology in the past decade and the responses this department has taken to meet these opportunities and challenges. Sections IIE and IIF consider criteria for evaluation of our research and educational programs and provide an assessment of the quality of our present research activities and graduate program. This information covers points IV.A to IV.C listed in the *Self-Study Guidelines* format. In this Section, we consider upcoming changes in research and graduate education in Pharmacology and our planned responses to them, as requested in items IV.D. to IV.G. of the *Self-Study Guidelines*.

Expected Changes in Research and Graduate Education

Genomics and Proteomics

Like all disciplines in the biomedical sciences, Pharmacology will be influenced in important ways by the completion of the sequencing of the human genome and the genomes of the mouse and other experimental animals. Efforts to understand the structure and function of the proteins encoded by the full complement of genes (the proteome) will be equally influential. Eventually, these experiments will lead to identification of all of the targets of drugs, hormones; and signal transduction pathways that are the focus of study in our research programs. How can we effectively take advantage of these new research opportunities? We plan to add two new experimental capabilities to research in our department to open these new opportunities for our research programs—analysis of gene expression using DNA arrays and analysis, interpretation, and prediction of protein structure of key signal transduction proteins.

DNA array technology. Based on research funding from NIH provided through the Population Research Center of the University of Washington, Dr. Stan McKnight will soon establish a capability for analysis of gene expression by use of DNA arrays. In addition, Dr. Randy Moon is working with RIKEN in Japan to develop array methods for developmental biology. This new approach will allow analysis of expression of hundreds of known genes in a single measurement. Array analysis can report relative gene expression data before and after cell stimulation and can provide comparative data for gene expression in normal and mutant animals or in samples from normal individuals and patients with specific diseases or drug therapies. We expect this new technology to open up important new research avenues in molecular pharmacology, cellular regulation, neurobiology, and other areas of research emphasis in this department.

Protein structure. Determining the primary structures of the full set of proteins encoded in the genome will further emphasize the importance of determination, analysis, and prediction of protein three-dimensional structures in all areas of biomedical research. Advances in methods for high-level protein expression and in methods for structural analysis of both minor proteins and insoluble membrane proteins promise to allow protein structure determination to become a more widespread part of research programs in the areas of interest of this department. Improved computer-based methods for structure comparison and prediction will allow available structural information to be used more incisively in studies of protein structure and function. We anticipate that these methods will be as much a part of biomedical research in ten years as molecular biology methods are now. To provide increased capabilities for this department in structural biology, we are in the process of re-organizing the Protein Core laboratory of the Molecular Pharmacology Facility to provide support for high level protein expression, protein crystallization, and computer-based structure comparison and analysis. We hope that these new initiatives will be as successful in supporting research programs in the department as previous establishment of peptide synthesis and protein sequencing capabilities of the Protein Core laboratory have been.

Molecular Mechanisms in Behavior and Drug Abuse

In recent years, there has been increasing success in understanding signal transduction mechanisms underlying learning, memory, fear conditioning, and other aspects of animal behavior that can be assessed in rodents. A key experimental approach in this regard has been the use of mouse genetic techniques, and Dr. Dan Storm and Dr. Stan McKnight of this department have been leaders in exploring the role of calcium/calmodulin-regulated adenylyl cycl,ase and cAMP-dependent protein kinase in these important neuronal processes. These studies open new avenues of research for the future. We intend to capitalize on these in our research and education programs by further emphasis on mouse genetic approaches to create animals with altered signal transduction pathways and analyze their behavioral alterations. We also intend to extend this general experimental approach to studies of drug abuse. Addiction, tolerance, and withdrawal from drugs of abuse are unique pharmacological phenomena that are likely related to persistent alterations in cellular signal transduction pathways in the brain. They are very amenable to the same experimental approaches that have been used successfully in this department and elsewhere to study the molecular basis of behavior. We plan to emphasize this area of research further by establishment of a research center devoted to these activities.

Center for the Molecular Basis of Drug Abuse. To bridge the gap between molecular and behavioral studies, we have developed a new Center for the Molecular Basis of Drug Abuse designed to identify the effects of targeted genetic mutations on mouse behavioral responses to opiates, cannabinoids and psychostimulants. Dr. Charles Chavkin will take the lead in establishing this Center. Its research will be built around Dr. Chavkin's work on opiates, Dr. Nephi Stella's research on cannabinoid action and the work of many faculty members on basic mechanisms of signal transduction. This research program builds on our strength in the analysis of signal transduction mechanisms and extends that research in an integrative systems direction. Besides enhancing the existing strong collaborations between laboratories in our program, the Center will enhance training of pharmacology graduate students interested in exploring the molecular basis of behavior. Funding for this Center comes from the National Institute on Drug Abuse, NIH and the Alcohol and Drug Abuse Institute at the University of Washington.

Graduate Student Preparation for Careers

An increasing fraction of our graduate students express interest in careers in biotechnology, the pharmaceutical industry, or science administration. Graduate students are exposed to academic careers on a daily basis as they carry out their dissertation research in laboratories and serve as teaching assistants in classes. In contrast, careers in the biotechnology and pharmaceutical industries or in science regulatory agencies are equally likely outcomes for our students. We believe that the broad research training and critical thinking developed in our graduate program will serve our students well in academic, industrial, or research administration settings, but their ability to make an informed choice about their careers requires broader exposure to these alternative career paths. Toward this end, we have instituted new mechanisms for providing students information on these diverse research careers in collaboration with other departments and programs. In collaboration with the Department of Medicinal Chemistry and the Department of Pharmaceutics of the School of Pharmacy, and partially supported by our joint Pharmacological Sciences Training Grant, we have initiated a program of speakers from the pharmaceutical industry and the biotechnology industry whose visits are organized to include informal discussion of career opportunities with graduate students. In collaboration with the Molecular and Cellular Biology Program, we have begun participation in an internship program that allows graduate students to spend one quarter on a rotation research project in a local company. We hope that these two measures will provide a clearer perspective for our graduate students on their choice of career paths.

Space, Budget, and Accountability

Like many successful academic programs at the University of Washington, the scope, impact, and quality of our research and educational programs are limited primarily by space and institutional resources. All of our research and administrative space is used to capacity. Approximately 190 faculty, students, postdoctoral fellows, and staff work in 27,900 sq. ft. of total space, including space for equipment and common facilities. The average of 147 sq. ft. per person is too low for optimal research productivity and prevents needed expansion of present research programs as well as planned development of new research activities. The university component of our departmental budget (not including the small fractional return of indirect costs from grants to the department) accounts for 15% of our total budget. Thus, every institutional dollar is leveraged by $7 M of extramural funding and total extramural funding from all sources totals $8.5 M. Further expansion of our departmental research and educational programs based solely on extramural funding would be perilous for the long-term stability of our programs. Thus, substantial increases in the scope and quality of our academic programs require additional budgetary and space resources. The developmental plan for the Department of Pharmacology proposes to add three faculty members and 7,500 sq. ft. of space in the coming decade to sustain departmental programs and respond to new opportunities in research and education. These modest additions to our program will allow us to add new research activities in genomics and structural biology and thereby participate more fully in the upcoming new directions in biomedical research.

Beyond the need for increased space and budgetary resources, the university has other opportunities to help our department and other research-intensive programs sustain and enhance their research and educational quality. Although restricted budgets prevent provision of additional resources for program enhancement, the university can provide increased stability, increased flexibility, and reduced administrative burden for use of its limited funds. Increased stability and flexibility and reduced requirements for administrative applications for funds and for generation of reports on use of funds have real financial value to programs that are strapped to provide administrative staff support for their activities. Since research space on the main UW campus is restricted and does not allow program expansion, the university can provide mechanisms and incentives for development of research space for extramurally funded programs in new research sites where an increased presence of UW-based research activities may be welcome. University administrative support for development of substantial research activities at a new site or sites may allow creation of a new critical mass of research activities that will enhance the scope and quality of research and educational programs.

The university can also provide more support for successful programs to generate stable, renewable forms of financial support themselves. In the case of our department, more effective university support for private fund-raising for endowments and more effective support for development of research funds derived from technology transfer would be very beneficial and would allow us to contribute more substantially to the long-term budgetary needs of our research and educational programs. To the extent that university policies direct such funds away from the departments and programs where they originate, they prevent successful programs from providing the financial support they need for continued success in the face of restricted budgets.

Accountability for the use of university resources in the Department of Pharmacology can be most directly addressed in terms of the high yield of quality research and education for the limited budget provided. Although the Department of Pharmacology is below average for the size of its faculty (12 university-funded faculty positions) and for the size of its institutional budget compared to its peers, its research and educational programs are rated in the top 5% of pharmacology departments nationally. We believe that comparison to peer departments is the most appropriate standard for addressing accountability as well as for addressing quality. Our research and educational programs are highly ranked according to this standard, and we hope that future development will enhance their quality.

Strategies to Assure Broad Demographic Representation

At the faculty level, our department is under-represented with respect to minorities and women, as are most basic biomedical science departments nationally. In the past decade, two of our three faculty appointments in university-funded positions have been women—Dr. Sandra Bajjalieh and Dr. Edith Wang. In addition, our only new appointment as a joint faculty member is Dr. Rejean Idzerda, an outstanding graduate of our department who is now Associate Professor of Medicine and Pharmacology. These new appointments both enhance our research and education programs and broaden our faculty representation. Regrettably, we have not been successful in identifying highly qualified minority candidates to consider in these recent faculty recruitments. This primarily reflects a very small pool of highly qualified minority applicants for faculty positions in pharmacology in the national pool.

As a step toward enhancing the pool of highly qualified minority candidates for faculty positions in biomedical science, graduate training programs supported by the National Institutes of Health require specific plans for recruitment of graduate students from minority groups that are under-represented in biomedical science. In keeping with this policy and with the goal of the

University of Washington to have an ethnically diverse student body and faculty, we have placed a high priority on identifying highly qualified students from minority backgrounds and from economically disadvantaged backgrounds, encouraging them to apply to our graduate program, and carefully considering their applications with respect to their qualifications and commitment to graduate study. Several approaches are used in this effort. Applicant lists are obtained from the MARC Fellows Program, which identifies highly qualified minority science students, and all of those students are contacted to solicit their interest in our graduate program. Graduate program information is also disseminated at the annual meeting of the MARC Scholars. Faculty members in the Department of Pharmacology participate in summer research programs that bring minority scholars to the University of Washington for a two-month research experience. The department also participates in the recently funded BRIDGES Program established by Associate Dean Dan Dorsa, a member of our departmental faculty, which provides academic support and enrichment for minority students in our graduate programs at UW. In recent years, an average of approximately 10% of our entering graduate students have been from minority backgrounds, up from less than 5% a decade ago. While this fraction is still too small, we hope that continued efforts will increase both the number of highly qualified applicants to our graduate program and the number of highly qualified minority applicants to pharmacology graduate programs nationally and will also increase the number of minority graduate successfully recruited into our graduate program. *Table 5. Application and Admissions Statistics 1990 - 1999* lists the application and admission statistics for minority applicants for the last decade.

Table 5. Application and Admission Statistics 1990 - 1999

	Applications		Offers		Entering	
Year	Total	Minority	Total	Minority	Total	Minority
1999	69	10	14	2	6	2
1998	50	13	11	1	7	1
1997	63	8	9	1	9	1
1996	68	8	6	0	6	0
1995	73	14	9	1	7	1
1994	59	11	9	2	6	2
1993	61	11	7	1	7	1
1992	54	9	10	4	9	2
1991	63	9	8	0	5	0
1990	50	8	9	1	9	1

Faculty Mentoring and Productivity

The faculty members of the Department of Pharmacology are highly productive by comparison with their peers nationally, as noted above. This high productivity is reflected in their level and quality of research activity as well as their level and quality of teaching activity. To sustain this high level of faculty productivity, the department conducts an annual review of faculty activity by peers within the department, and the Chair meets with each faculty member to encourage his or her continued efforts to provide the highest levels of research and educational activities that are possible with existing resources. Whenever possible, research productivity is recognized by expansion of research space to allow further program development, and research and educational productivity is recognized by merit salary increases when provided by the university. Mentoring of junior faculty members is the dual responsibility of the Chair and two designated senior faculty mentors whose research and teaching expertise is appropriate for the new faculty member. This two-pronged approach provides for a more formal approach by the Chair in scheduled meetings and a more informal, day-to-day approach by senior faculty colleagues.

V. Goals

The goals of the Department of Pharmacology in the next decade are to sustain the high quality programs that are in place at present and to respond effectively to new opportunities in research and education in our discipline and in the biomedical sciences generally. More specifically, our goals are as follows:

1. **To improve our education of health science professional students.** We plan expansion of our courses in the medical curriculum using internet-based teaching methods as well as revisions and improvements of our courses for dental and pharmacy students.

2. **To broaden and enhance the research program of the Department of Pharmacology.** We plan to add new faculty members with expertise in genomics and structural biology related to pharmacology. We will establish DNA array technology in the DNA Core of the Molecular Pharmacology Facility. We will also establish high yield protein expression and effective interfaces with structure determination in the Protein Core of our Molecular Pharmacology Facility. New research technologies will also be added to the individual research programs of our faculty as needed to sustain their leadership in their research areas.

3. **To improve the Graduate Program in Pharmacology.** We plan to increase the range of our research training by incorporating new research directions in genomics and structural biology related to pharmacology, appointing additional primary and affiliated faculty in expanding areas of our discipline, and providing new opportunities for our students to intersect with the biotechnology and pharmaceutical industries. New advanced graduate seminar courses will be added to our curriculum to reflect the expertise of new faculty members and to respond to new opportunities in our discipline.

4. **To increase the participation of the Department of Pharmacology in interdisciplinary graduate programs related to our discipline.** We plan to increase our participation in both the Graduate Program in Neurobiology and the Molecular and Cellular Biology Program by increasing the teaching by Pharmacology faculty members in the curricula of these programs and by interacting more extensively with these graduate students. In addition, we plan to begin to participate in the Graduate Program in Biomolecular Structure and Design through new faculty appointments with expertise in this research area.