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PROGRAM OVERVIEW

The graduate program leading to the Ph.D. degree in Pharmacology is designed to provide the strong background in research methodology and experimental design necessary for a professional career in academia, industry or governmental service. Generally five years are required to complete the requirements for the Ph.D.

Students are expected to complete the required course work and complete the qualifying examination for the Ph.D. by the Summer session of their second year. Following successful completion of all required courses and the qualifying examination and satisfactory research progress, students are admitted to candidacy for the Ph.D. During the third year, students are expected to develop a dissertation research proposal and present it at a departmental seminar. Students are encouraged to present at a departmental seminar each year and to make presentations of their research data at national scientific meetings.

Disclaimer

The provisions of this Handbook do not constitute a contract, expressed or implied, between any applicant, student, or faculty member and the Department of Pharmacology, the Graduate School of Biomedical Sciences, The University of Texas Health Science Center at San Antonio, or The University of Texas System. The Department of Pharmacology reserves the right to alter course offerings at any time or to change the curriculum or any other procedures leading to the awarding of a degree and any other requirements affecting students. Changes will become effective whenever the proper authorities so determine. The changes will apply to prospective students and may apply to those already enrolled.

Revisions

Recommendations for improving the content of this handbook are welcomed from the students and any members of the faculty of the Department of Pharmacology.

Abbreviations and Definitions Used in this Publication

Dean  Dean of the Graduate School of Biomedical Sciences
UTHSCSA  The University of Texas Health Science Center at San Antonio
GSBS  Graduate School of Biomedical Sciences
GFC  Graduate Faculty Council
COGS  Committee on Graduate Studies of the Department of Pharmacology
Faculty  Unless noted otherwise, Graduate Faculty of the Department of Pharmacology
ACADEMIC STANDARDS

Students majoring in pharmacology are expected to maintain a Satisfactory (S) grade in Seminar, Research, Dissertation, Supervised Teaching and Special Topics and at least a letter grade of B in all of their graduate courses.

GSBS guidelines state that a student must maintain a cumulative GPA of 3.0. A student, whose cumulative GPA falls below 3.0, is automatically placed on probation by the Dean and warned that continuation in the graduate program is in jeopardy. While on probation, the student must maintain a ‘B’ average in all subsequent semesters for which he or she is registered. Failure to achieve a 3.0 in the course work for any semester could result in the student being considered for dismissal from the Graduate School by the COGS and/or the Dean. A student will remain on probation as long as the cumulative GPA remains below 3.0. A student may not withdraw from any courses while on academic probation.

If a letter grade of C or U is received in any pharmacology course, the student will be referred to COGS for consideration. Generally, the student will be required to repeat the course. A letter grade of C in two or more graduate courses or a letter grade of D in any graduate course could result in COGS recommending that the student be dismissed from the graduate program. COGS will decide on the appropriate course of action following a review of each case.

Appeal Process

A student may appeal to COGS to reconsider any policy decision that may affect the student’s progress or tenure in the Pharmacology Graduate Program. In those cases where dismissal is recommended to the Dean, the student may appeal to COGS to reconsider its recommendation for dismissal. If COGS still recommends dismissal from the graduate program, then the student may appeal to GFC to reconsider the recommendation.

COURSE WORK AND LABORATORY ROTATIONS

Required Courses

All students enrolled in the Ph.D. program in Pharmacology are required to take the following courses:

<table>
<thead>
<tr>
<th>Course Code</th>
<th>Course Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSBL 5095</td>
<td>Experimental Design and Data Analysis (Statistics)</td>
</tr>
<tr>
<td>INTD 5005</td>
<td>Core Course I: Biochemistry</td>
</tr>
<tr>
<td>INTD 5006</td>
<td>Core Course II: Molecular Biology</td>
</tr>
<tr>
<td>INTD 5007</td>
<td>Core Course III: Cellular Biology</td>
</tr>
<tr>
<td>INTD 6002</td>
<td>Ethics</td>
</tr>
</tbody>
</table>
PHAR 5001     Pharmacology
PHAR 5013    Principles of Pharmacology
PHAR 5020    Basics of Research Design
PHAR 5090    Pharmacology Seminar
PHAR 5092    Special Problems in Pharmacology/Laboratory Rotations (two
              semesters required)
PHAR 6071    Supervised Teaching in Pharmacology
PHAR 6097    Research
PHAR 7099    Dissertation (2 semesters required)
PHAR ------  4 credits of Electives (minimum)

Exemptions

An exemption from any of the courses listed above may be requested if the student has
taken similar courses and received at least a letter grade of ‘B’. The student should
petition COGS as soon as possible after admission to the graduate program for
exemption from a given course. An exemption examination in Biochemistry is offered
during the first week of each Fall semester.

TYPICAL COURSE SCHEDULE FOR THE FIRST TWO YEARS

Fall Semester First Year

<table>
<thead>
<tr>
<th>Course Number</th>
<th>Course Title</th>
<th>Credit Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTD 5005</td>
<td>Core Course I: Biochemistry</td>
<td>4.0</td>
</tr>
<tr>
<td>INTD 5006</td>
<td>Core Course II: Molecular Biology</td>
<td>4.0</td>
</tr>
<tr>
<td>PHAR 5013</td>
<td>Principles of Pharmacology</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>Orientation to PHARM Graduate Studies</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Introduction to Lab Rotations</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td><strong>TOTAL</strong></td>
<td><strong>11.0</strong></td>
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Spring Semester First Year

<table>
<thead>
<tr>
<th>Course Number</th>
<th>Course Title</th>
<th>Credit Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTD 5007</td>
<td>Core Course III: Cellular Biology</td>
<td>4.0</td>
</tr>
<tr>
<td>PHAR 5001</td>
<td>Pharmacology</td>
<td>4.0</td>
</tr>
<tr>
<td>PHAR 5092</td>
<td>Special Problems: Laboratory Rotation</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td><strong>TOTAL</strong></td>
<td><strong>9.0</strong></td>
</tr>
</tbody>
</table>
### Summer Semester First Year

<table>
<thead>
<tr>
<th>Course Number</th>
<th>Course Title</th>
<th>Credit Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHAR 5020</td>
<td>Basics of Research Design</td>
<td>1.5</td>
</tr>
<tr>
<td>PHAR 5092</td>
<td>Special Problems: Laboratory Rotation</td>
<td>1.0</td>
</tr>
<tr>
<td>PHAR 6097</td>
<td>Pre-dissertation Research</td>
<td>3.5</td>
</tr>
</tbody>
</table>

**TOTAL** 6.0

### Fall Semester Second Year

<table>
<thead>
<tr>
<th>Course Number</th>
<th>Course Title</th>
<th>Credit Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSBL 5095</td>
<td>Experimental Design and Analysis</td>
<td>2.0</td>
</tr>
<tr>
<td>PHAR 5090</td>
<td>Seminar</td>
<td>1.0</td>
</tr>
<tr>
<td>PHAR 5091*</td>
<td>Special Topics: Micro-Electives</td>
<td>---</td>
</tr>
<tr>
<td>PHAR 6097</td>
<td>Pre-dissertation Research</td>
<td>---</td>
</tr>
</tbody>
</table>

**TOTAL** 9.0

### Spring Semester Second Year

<table>
<thead>
<tr>
<th>Course Number</th>
<th>Course Title</th>
<th>Credit Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTD 6002</td>
<td>Ethics in Scientific Research</td>
<td>0.5</td>
</tr>
<tr>
<td>PHAR 5091*</td>
<td>Special Topics: Micro-Electives</td>
<td>---</td>
</tr>
<tr>
<td>PHAR 6097</td>
<td>Pre-Dissertation Research</td>
<td>---</td>
</tr>
</tbody>
</table>

**QUALIFYING EXAM** (see pages 11-18 for details)

**TOTAL** 9.0

*A total of 4 credit hours of Electives/Micro-electives are required. These credits should be obtained by the end of the second year.

### Summer Semester Second Year

<table>
<thead>
<tr>
<th>Course Number</th>
<th>Course Title</th>
<th>Credit Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHAR 6097</td>
<td>Pre-dissertation Research</td>
<td>6.0</td>
</tr>
</tbody>
</table>

**TOTAL** 6.0
LABORATORY ROTATIONS

Students must complete two laboratory rotations in different laboratories by the end of their first year in the graduate program. Each rotation is a full-semester rotation and students are required to write a report and to present a 15-minute post-rotation talk following the completion of each laboratory rotation. Students are encouraged to work with their Lab Rotation supervisor who will assist them in the preparation and organization of the oral presentation. At the beginning of the rotation, the Lab Rotation supervisor will discuss the criteria (below) that will be used to evaluate the performance of the student during the laboratory rotation. The Graduate Program Coordinator will provide a written copy to all students at the beginning of the rotation.

Entering students have the option of beginning their graduate training early by undertaking a rotation in the summer semester prior to the first year of classes.

Students are expected to spend at least 12 hours per week in their laboratory rotations during the fall and spring semester rotations and work full-time during the Summer semester rotation. The project should be terminated at least one week prior to the end of the semester to give the student time to prepare the written report on the project and present their post-rotation talk. Completion of the rotation may not be extended into the next semester, including the completion of the written report.

At the end of the rotation, students write a short report (about 10 double-spaced, typewritten pages) in journal style (i.e. Introduction, Methods, Results and Discussion). One copy of the report is given to the Lab Rotation supervisor for evaluation and grading (see below), and a second copy is given to the Graduate Academic Coordinator to serve as a file copy.

Lab rotation supervisors must be selected from the Graduate Faculty of the Pharmacology Graduate Program who have active research laboratories.

Special Problems Project Criteria

a. The Objective

The objective of the lab rotation is two-fold:

1. To give students an opportunity to develop research skills and aid them in selecting a laboratory in which to pursue their dissertation research.

2. To permit faculty to evaluate the laboratory skills and potential research aptitude of the student.
b. The Project

The design of rotation projects is the responsibility of the mentor and should be done prior to accepting a student in the laboratory. The research project need not be an original research investigation. It can be an extension of some experiment that is performed routinely in the mentor’s laboratory or some methodology that is feasible for a student to complete in the allotted time. It is critical that the mentor supervising the project develop a concise and well-defined project for the student. The project should satisfy the following criteria:

1. The project should be hypothesis-driven.
2. The methodology required to complete the project should currently be in use in the laboratory.
3. There should be a reasonable expectation of some success within the allotted time.

c. The Evaluation

The student will be evaluated on the following criteria:

1. Technical competence
2. Motivation
3. Understanding of the techniques and instrumentation used in the rotation.
4. Understanding of scientific concepts and principles pertinent to the project.
5. Ability to read and critically evaluate literature.
6. Ability to work, think and write independently.

The mentor should meet regularly with the student to discuss the student’s performance based on the above criteria. At the end of the rotation period, a rotation evaluation form (page A-1) will be sent to the mentor. The mentor will give the student an A (excellent), B (average) or C (unsatisfactory) grade for each criterion.

The mentor must meet with the student to discuss the evaluation and have the student sign the evaluation form to indicate that he/she has had the opportunity to review and discuss the evaluation with the mentor. The evaluation is then submitted to the Chair of COGS. These evaluations are then placed in the student's file and are available for review by the faculty.

d. The Written Report

The report is to be given to the mentor before the end of the semester. The written report is to follow the format of a short research communication (about 10, double-spaced, typewritten pages) consisting of the following parts:

1. Introduction
2. Methods
3. Experimental Results
4. Discussion
5. Summary and Conclusions
6. References (no more than 10 – 12 references)

Each student should prepare two copies of the written report; one copy is to be given to the Graduate Program Coordinator to be kept as a file copy and the other copy is to be graded by the supervising faculty member.

e. The Post-Rotation Talk:

Students are required to give a brief (approximately 15 minutes) post-rotation talk to the Department on the research project that should state the hypothesis tested, cite specific objectives, give a brief discussion of the methodology employed and summarize the results obtained in the study. Among those in attendance, members of the Department will be asked to complete Seminar Speaker Critique forms (page A-2) to provide constructive criticism to the speakers. In addition, the presentations will be video-taped. The video tape will be provided to the student for his/her own viewing. It is suggested that the student review the tape and discuss the critique forms with his/her mentor.

f. The Grade:

Students receive a letter grade for each semester of Special Problems that is based equally upon the evaluation of the student's performance in the laboratory (50%) and on the written report (50%).

REGISTRATION

The Registrar’s Office will notify students via e-mail of the dates open for web-based registration. Prior to registering, students should obtain any necessary permit numbers from the Graduate Academic Coordinator.

To be enrolled as a full-time student for the Fall and Spring semesters, students must register for a minimum of 9 credit hours; for the Summer semester, students must register for a minimum of 6 credit hours.

At the time of registration for each Fall semester, students should also submit a UTHSCSA Health Insurance Coverage Information form to the Registrar's Office to show proof of health insurance coverage. This form is not required for subsequent terms throughout the year unless there is a change in coverage.

Registering for Final Credit Hours

A student may register for final credit hours during the semester or summer session s/he plans on defending her/his dissertation. A student registering for final hours is exempt from the minimum tuition requirement and only required to pay tuition for 3 credit hours.
THE PH.D. QUALIFYING EXAMINATION

Passing the qualifying examination is one of the steps required for advancement to candidacy. The other steps are satisfactory completion of all required courses (average GPA of at least 3.0) and certification by the supervising professor that the student has demonstrated the potential for productive and independent investigation. The examination includes both a written and an oral component.

Objective
The overall objective of the examination is to determine whether the student has a sufficient basis of knowledge, a command of the scientific method, and originality of thought necessary for advancement to the subsequent phase of mentored, thesis work as a Ph.D. candidate.

Specific objectives include assessment of the capacity of a student to: 1) assemble a database of knowledge on a particular topic; 2) use that database of knowledge to develop a focused and original research question and to propose specific testable hypotheses; 3) use the scientific method to design experiments to test the proposed hypotheses; 4) propose methods to evaluate the anticipated results of the experiments and consider alternative approaches; and 5) to communicate both orally and in writing.

Responsibilities of the Faculty Advisor
A student is encouraged to request that a member of the Pharmacology graduate faculty serve as an advisor during the preparation for the examination. The faculty advisor will attend the oral examination as a non-participating, non-voting observer. The role of the faculty advisor will be to serve as a consultant to provide the student with general guidance in preparation of the proposal. The faculty advisor should advise the student whether the proposal is generally ready for distribution (i.e., thorough, well researched, generally accurate, etc.). The faculty advisor will not play an active role in the formulation of the research proposal and should not suggest specific goals, experiments, methods or analyses. The responsibility for the quality of the proposal in terms of originality, approach to solving the problem or testing the hypotheses, and significance rests completely with the student. The student may give an original interpretation or a re-interpretation of literature data, propose a series of experiments to test a hypothesis, or present a new theoretical approach to a problem.

The Examination Committee
The examination committee will comprise four graduate faculty members from the Department of Pharmacology and one graduate faculty member from another department at UTHSCSA. The examination committee will be chosen by the COGS who will select one of the four Department members to serve as chairperson.

Responsibilities of the Examination Committee
- Determine the initial feasibility of the proposal based on the student’s outline
• Determine if the written proposal provides an adequate basis for an oral examination
• Provide the student with written comments/recommendations (in the event that the initial written proposal is not deemed suitable for defense)
• Sign the “Petition for Oral Examination” upon approval of the written proposal
• Conduct the oral examination
• Determine whether or not the student has satisfactorily defended his/her written proposal
• Sign the “Petition for Admission to Candidacy” or, in the event that the defense has been deemed unsatisfactory, provide the student with feedback that outlines specific aspects of the student’s performance that need improvement in a second examination.

Responsibilities of the student
• Discuss ideas about a proposal with a faculty advisor
• Write and submit to the examination committee an outline of a proposal
• Write and submit to the examination committee an original proposal
• Present a copy of the proposal with a signed Petition for Oral Examination form to the COGS chair when the committee has approved the proposal
• Inform the COGS chair of the date of the oral examination
• Defend the proposal to the examination committee in an oral examination
• Consult with the faculty advisor regarding the commitment of time and insure that all other research and academic responsibilities are met

Scheduling
Except under special circumstance, approved by the COGS, the examination must be completed by 30 June in the summer following the second academic year. If a student enters the program in January, the deadline will be extended to 28 February in the second academic year. The student is responsible for scheduling all activities related to the examination.

Suggested Timeline
● Choose a faculty advisor and discuss possible topics in January (2nd year)
● Submit outline by 1 February
● Prepare written proposal during February and March
● Submit final proposal by 1 April
● Complete oral examination by 1 June
● Should a retest be necessary, both components of the examination (written and oral) must be completed by 30 June. If a student fails to successfully complete the qualifying examination by this deadline, his/her progress will be reviewed by COGS with the possibility of suspension of stipend or dismissal from the program.

General Guidelines for the Preparation of the Written Proposal to be used as the Basis of the Oral Examination
  a) The written component will comprise an NIH NRSA-style research
proposal written on any acceptable topic related to pharmacology. It is permissible for the student to choose a topic in the area in which he/she plans to do his/her dissertation studies.

b) The proposal must include hypothesis-guided experiments. The experiments should be designed to produce results, which clearly support or reject the associated hypotheses. It is not acceptable to propose experiments that are likely to yield equivocal results that will not discriminate between the truth or fallacy of the hypothesis. It is not acceptable to list a hypothesis that one cannot imagine to be false. It is not acceptable to propose purely descriptive experiments (i.e., I'll do this and see what happens.).

c) The proposal should describe a project that one person could execute in about two years of work.

d) The experiments proposed should be the logical next steps in some area, or should reinforce and extend recent advances in the area.

Format of the Written Proposal
a) The text can not exceed 10 single-spaced typed pages, including figures and tables. Figures should have a title and a legend. Tables should have a title and an explanatory footnote. Figures and tables should be numbered as referenced in the text. Include attribution in the legend if a figure has been copied from elsewhere. Hand-drawn diagrams are acceptable so long as they reproduce legibly. Figures may be annotated to make your point more clear. Preliminary results are not expected. The proposal should have a cover page with a title and names of the student, faculty advisor, and examination committee members. A suggested breakdown for the text is as follows:

  Abstract: ½ page
  Specific Aims with Hypotheses: ≤ 1 page
  Background & Significance: 2-4 pages
  Experimental Design & Methods: 2-4 pages
  Literature Cited: Not included in the 10-page limit

b) Observe NRSA Guidelines:
- At least 0.5 inch margins on all sides
- Number all pages
- Place name on all pages
- At least 10 point font (Helvetica or Arial 12 point is suggested)
- Type density, including characters and spaces, can not exceed 15 characters per inch
- References are unlimited and should be cited from the text by author and year
c) The proposal must not contain text that is extensively quoted or paraphrased from any other work. Any quoted material must be given proper attribution.

Content of Specific Sections

a) **Abstract** The abstract should provide an overview of the entire project including: 1) Background; 2) Hypotheses; 3) Aims; 4) Experimental Approaches and 5) Significance.

b) **Specific Aims** Each (usually 2-4) should be summarized in a single numbered, explicit sentence associated with a short explanatory paragraph. At least one aim should be in the form: “Aim X is to test [hypothesis] by [experimental strategy].” Multiple aims could test the same hypothesis by different approaches, or test different hypotheses with the same collection of data. Some aims may be preparatory (i.e., to prepare a mutant protein, or to establish the power of a method on some test material, or to clone a gene); however, some of the aims must purpose studies that will test specific hypotheses.

c) **Background and Significance** Briefly discuss the background to the proposal, critically evaluate current knowledge, and specifically identify voids in the literature that the project will address. State concisely the importance of the research to longer-term objectives. An exhaustive survey of the literature and a lengthy bibliography are not required as part of the written proposal, although the student will be expected to demonstrate a thorough understanding of the relevant literature during the oral defense. In the written document, include only information that defines the problem and that justifies the proposed work.

d) **Experimental Design and Methods** Discuss the experimental design and the procedures to be used to accomplish the specific aims. Include the means by which the data will be analyzed and interpreted. Describe any new methodology and its advantage over existing methodologies. Discuss the potential difficulties and limitations of the proposed procedures and provide alternative approaches to achieve the aims.

The Experimental Design includes topics such as how many samples will be needed, what controls will be needed, and exactly what measurements will be the basis of determining whether or not the hypotheses are supported (accepted or rejected). Experimental Design often is best organized according to the aims. The Methods include precisely how an experiment is to be carried out. Methods may be included within the Experimental Design section; however, since the same methods are often used in several aims, it is sometimes more convenient to provide Methods in a separate section. Do not include an exhaustive list of details for Methods; rather give the name and purpose of the method, the reference you would follow and a brief discussion of how you will address any potential weaknesses in the methods. Do not invent new methods unless that is an explicit aim of the proposal. During the oral examination, the student will be expected to demonstrate a knowledge of the theory behind the methods.
This section often includes brief descriptions or discussions of the following: 1) future directions; 2) possible outcomes and potential problems and 3) expected timeline.

e) **Literature Cited** For each citation, provide the names of all authors, the article title, the name of the book or journal, volume number, page numbers, and year of publication. Arrange in alphabetical order by first author. If you cite a reference, you are expected to have read and understood it. The committee may request inclusion of a recent Medline, or the equivalent, literature search in addition to the cited literature.

**Oral Defense**
During the oral component of the examination, the committee members examine the student on the proposal and related areas of pharmacology. The oral component will consist of a brief (15-minute) formal presentation (e.g., PowerPoint) by the student that summarizes each of the elements of the proposal, followed by questions from and discussion with the examination committee.

**Grading**
Grading of the qualifying examination will be pass/fail and will be determined by the examination committee based on the student’s performance on two components of the examination. At least four of the five members of the examination committee must vote each component as pass for the student to successfully complete the examination.

**Specific Issues to be Assessed During Grading**
Does the student possess sufficient knowledge in the area of the examination? (Note: In the absence of remembering details, a perspective on what is known, where it might be found and how it might be applied usefully to the problem should be considered favorably as a basis of knowledge.)

Has the student demonstrated an understanding of fundamental pharmacological principles?

Has the student researched the specific background of the proposal well enough to understand the overall theory governing the work in this area? Can the student state how unexpected results would affect the current theory?

Does the student have an understanding of the theory underlying the specific methods proposed?

Can the student distinguish a hypothesis from a belief (a statement that the student cannot imagine being wrong)?

Can the student recognize when an experiment clearly rejects or supports a hypothesis? Does the student appreciate the implications of negative data?
Can the student identify and provide potential solutions for weaknesses in the proposal?
Does the student provide appropriate controls to address possible weaknesses?

Can the student discuss what future direction should be taken given some specified outcome of the proposed experiments?

**Specific Recommended Chronology of events**
Except under special circumstance, approved by the COGS, the examination must be completed by 30 June in the summer term following the second year. If a student enters the program in January, the deadline will be extended to 28 February. The examination will be considered failed if not completed by the deadline. Since several revisions of the proposal may be required, students are strongly encouraged to begin several months before the deadline.

1) The student chooses a general topic for the proposal, requests a member of the Pharmacology graduate faculty to serve as an advisor, and discusses the proposal topic with the faculty advisor in terms of general feasibility.

2) The student writes an outline of the proposal (maximum of two pages) and submits it to the chair of COGS who will convene a meeting of COGS to choose members of an examination committee and a committee chairperson. Each of the members of the examination committee will be given the outline.

3) **Three days** after distribution of the outline, the chairperson of the examination committee will solicit opinions from the other committee members concerning the feasibility of the proposed qualifying examination subject. The chairperson then consults with the student about the committee’s evaluation and either advises the student to write the full proposal (see below) or advises the student that the topic or specific aims do not form an adequate basis for a proposal. In the latter case, the student may re-write or submit a different outline for consideration. The preparation of an acceptable proposal is the responsibility of the student.

4) Upon being advised to continue, the student writes the full proposal taking into consideration any initial concerns/suggestions of the committee.

5) The student distributes the full proposal to the committee. After **two weeks**, the committee members consult with the chairperson of the committee as to whether or not the proposal is approved for oral defense. If the proposal is not approved, the student will receive from the chairperson of the examination committee written comments from each of the examination committee members. The student then may re-write the proposal on a new topic or modify the original proposal based on the comments and recommendations of the committee. Upon resubmission of the written component, the student will be advised that they have either 1) passed the written component, at which point they will schedule the oral component of the examination or 2) failed the
written component a second time, at which point they will be removed from consideration for advancement to candidacy. A proposal may be defensible (i.e. that it is based on testable hypotheses), but still be deficient (e.g. in experimental design or in scientific writing) such that a re-write is required. The student, not the committee, is responsible for generating an acceptable proposal. If serious flaws persist in the re-written proposal, the committee may approve the proposal for the oral exam and then question the student on the deficiencies of the proposal in the oral exam. Thus, “approval” of the written proposal does not guarantee that its content will be sufficient to pass the exam.

When the committee members approve the written proposal, they sign the “Petition for Oral Examination” form (page A-3). The student forwards the signed form and a copy of the proposal to the COGS chair. At this time, the student schedules the oral exam, which should be completed by 1 June in the summer following the second year. The committee is entitled to a two-week period between approval of the written proposal and the oral examination. The student may consult with committee members about material to be covered in the examination.

6) During the oral component of the examination, the committee members examine the student on the proposal and related areas of pharmacology. The committee will question the student until a consensus is reached that ample information is available on which to evaluate the student’s performance. A maximum of three hours will be allotted for the examination.

7) Approval of four of the five committee members is required for the student to pass the qualifying examination. Upon approval, examination committee members sign GSBS Form 32: Petition for Admission to Candidacy (page A-4) to substantiate that the student has passed the qualifying examination.

The student will be allowed to repeat the oral examination with the same committee one time if the student fails. The chairperson of the committee shall confer with the committee, the COGS chair, and faculty advisor to construct the requirements for the re-examination. They should agree on a format for a re-examination designed to allow the student to correct deficiencies revealed during the initial examination. The format may be a written follow-up with no oral examination, a repeat of the oral exam with no further writing, or both a re-write and a repeat oral examination. Within one week, the chairperson of the committee will give the student and the COGS chair a written explanation for the basis of the failure and provide guidelines to prepare for the re-examination. The re-examination must be completed within three months of the first examination and by the 30 June deadline. If the student fails the re-examination, the student will be removed from consideration for advancement to candidacy.
8) Upon completion of the qualifying examination, satisfactory completion of all required courses, certification by the Supervising Professor that the student has clearly demonstrated the potential for productive and independent investigation, and receipt of GSBS Form 32 (page A-4), COGS will decide whether to recommend to the Associate Dean of the Graduate School that the student be admitted to candidacy for the Ph.D. degree. The Associate Dean makes the final decision on admission to candidacy for the Ph.D. degree.

ADMISSION TO CANDIDACY

Requirements for Admission to Candidacy

1. Satisfactory completion of all required courses.
2. A cumulative GPA of at least 3.0 in all course work undertaken since matriculation in the program.
3. A report by the chair of COGS that the student has passed the qualifying examination.
4. A report by the student's chosen dissertation supervisor that the student has clearly demonstrated the potential for productive and independent investigation.
5. If the overall evaluation of the eligibility of the student for admission to candidacy for the Ph.D. degree is favorable, then COGS votes on approval of admission of the student to candidacy. The chair of the COGS then submits a Petition for Admission to Candidacy for the degree of Doctor of Philosophy Form (page A-4) to the Dean for approval.
6. If approved, the student receives an official notification of admission to candidacy from the Dean of the Graduate School (GSBS Form 35).

DISSERTATION

Selection of the Supervising Professor

Students are encouraged to select a member of the Pharmacology Graduate Faculty who will serve as the supervising professor for his/her dissertation research as early as possible after completing the required lab rotations. The student is required to petition the COGS in writing for approval of the proposed dissertation supervisor. The faculty member must have an active research lab, be willing to serve as the student’s dissertation supervisor and must have funds to support the student’s stipend and research activities for the entire time required to complete the dissertation research.
project (usually 3 years). COGS will not approve a faculty member as a dissertation supervisor who does not have funds to support the student’s research and stipend.

Selection of the Temporary Supervising Committee

A Temporary Supervising Committee should be formed to assist the student in preparing the dissertation research proposal. This committee should be formed as soon as possible after the student has chosen a mentor, but no later than three months after the student’s Admission to Candidacy. The members of this committee are selected according to the mutual agreement of the student, the supervising professor and the prospective committee members. The supervising professor must submit to COGS the 'Department of Pharmacology Temporary Dissertation Supervising Committee Form' (page A-5) that lists the members of this committee. COGS will vote to approve the committee or make recommendations for changes in the committee to the supervising professor. In most instances, members of the Temporary Supervising Committee become members of the permanent supervising committee.

The temporary supervising committee must consist of at least four members:

1. the supervising professor, who serves as the chair of the supervising committee.
2. two additional members from the Graduate Faculty of the Pharmacology Graduate Program.
3. one member who must be a faculty member at UTHSCSA but not a member of the Pharmacology Graduate Program.

Preparation of the Dissertation Proposal

During the first year following admission to candidacy, the student should prepare his/her dissertation proposal in the format of a National Research Service Award (NRSA) grant proposal and submit the proposal to the Temporary Dissertation Supervising Committee for approval. The format for an NRSA is presented below. Additional information on NRSA grants can be obtained from the NIH’s website (www.nih.gov).

Students should include sufficient information in their proposal to permit an effective review without reviewers needing to refer to the literature. Brevity and clarity in the presentation are considered indicative of a student’s approach and ability to conduct a superior project. The entire proposal is not to exceed 10 pages including all tables and figures. The format for the proposal is as follows:

1. Specific Aims - State the specific purposes of the research proposal and the hypotheses to be tested.
2. Background and Significance - Sketch briefly the background to the proposal. State concisely the importance of the research described in this application by relating the specific aims to broad, long-term objectives.

3. Research Design and Methods - Provide an outline of:

   o Research design and the procedures to be used to accomplish the specific aims;

   o Tentative sequence for the investigation;

   o Statistical procedures by which the data will be analyzed

4. Potential experimental difficulties should be discussed along with alternative approaches that could achieve the desired aims.

Once the committee approves the proposal, the student will present the proposal to the Pharmacology Faculty as a departmental seminar and defend the proposal in a COGS meeting following the seminar presentation.

The COGS must approve each student's dissertation proposal and Permanent Supervising Committee.

Procedures - Temporary Supervising Committee

The Temporary Supervising Committee must first approve the dissertation research proposal and sign the 'Department of Pharmacology Approval of Research Proposal Form' (page A-6). The student submits this form to the Graduate Program Coordinator. The student schedules a seminar at which s/he presents the dissertation research proposal to the Pharmacology Faculty. The student gives a copy of the approved written dissertation proposal to the Graduate Program Coordinator to distribute to each member of COGS at least one week in advance of the presentation of the dissertation research proposal at a departmental seminar.

Procedures - COGS

The student defends her/his dissertation research proposal to COGS at a meeting of COGS after her/his dissertation proposal seminar. During the defense, the supervising professor is present as a quiescent observer. Following the defense, the student is excused from the room and the supervising professor has the opportunity to share comments about the proposal made by the Temporary Supervising Committee. Following discussion and approval of the dissertation research proposal by the COGS,
the Supervising Professor presents and describes the qualifications of the proposed membership of the permanent committee.

The Permanent Supervising Committee must consist of at least five members. The Supervising Professor serves as the chair of the supervising committee. Four of the members must be from UTHSCSA (the supervising professor, 2 members from the Pharmacology graduate faculty and one other UTHSCSA). One member must be from an outside institution not affiliated with UTHSCSA. It is the responsibility of the supervising professor to contact the proposed external committee member to determine if the individual is willing to serve on the student's dissertation supervising committee. The supervising professor should provide the individual with a copy of the dissertation research proposal to review and request that s/he provide comments about the strengths and weaknesses of the proposal. Additional members may be added as deemed appropriate.

COGS votes on whether or not to approve the proposed membership of the Permanent Supervising Committee. The Chair of COGS prepares and sends the ‘Recommendation for Approval of Dissertation Research Proposal and Supervising Committee Form’ (page A-7) to the Dean signifying that COGS has reviewed and approved the dissertation research proposal and the Permanent Supervising Committee.

**SUPERVISION OF THE DISSERTATION RESEARCH**

**Dissertation Supervisory Committee Meetings**

The Dissertation Supervisory Committee (temporary or approved) is required by COGS to meet by the end of the term each fall and spring. The student will provide a written progress report to her/his committee prior to the meeting. The report should include what the student’s research aims were during the semester, the results of her/his research and how the student plans to proceed during the next reporting period. The report should not exceed six pages. The supervising professor is required to provide the Chair of COGS with a brief written report of the student's research progress (page A-8). If the Chair of the COGS does not receive a report of the student's progress by the end of the semester, the student will not be allowed to register for the subsequent semester. The scheduling of these meetings is the student’s responsibility.

Major changes in the research status of the candidate, such as the selection of a new supervising professor, new Supervising Committee Members or a substantive change in research direction, must be submitted to COGS for approval.

**Registration for Dissertation**

Students on the Ph.D. degree track may register for the Dissertation course (PHAR 7099) after the following actions have been taken:
• Approval of admission to candidacy for the Ph.D. degree by the Dean
• Approval of the dissertation research proposal by COGS and the Dean
• Approval of the membership of the candidate’s Supervising Committee by COGS and the Dean

A candidate for the Ph.D. degree must register for at least two terms of Dissertation credits. Only one of the terms may be a summer session.

Final Credit Hours
A student must be registered for the semester or summer term in which s/he graduates. If a student is registering for only final credit hours in preparation of a dissertation and registers for no other courses, s/he is exempt from the minimum tuition requirement and pays only tuition based upon the number of credit hours for which s/he registers. Such registration shall be considered a full-time course load. The minimum number of final credit hours for the Ph.D. degree is three. A student may register for final credit hours only once.

PREPARATION OF THE DISSERTATION

When the data collection is completed or close to completion, the student will request permission from the Supervising Committee to stop doing experiments and to begin writing the dissertation.

Selection of Dissertation Format

There are two formats that may be used for the Ph.D. dissertation: the Traditional Format and the Chapter Format. The Chapter Format is the default format for all Ph.D. dissertations. Students wishing to use the Traditional Format must receive the approval of both their supervising committee and of COGS.

The Chapter Format consists of the following sections:

a. Abstract
b. Table of Contents
c. General Introduction
d. Literature Review
e. Chapter I, II, III, etc.
f. General Discussion
g. Summary and Significance
h. References

Each chapter should be organized in the format of an article that would be published in a scientific journal as follows:
The **Traditional Format** consists of the following sections:

a. Abstract
b. Table of Contents
c. General Introduction
d. Literature Review (This may be combined with the Introduction.)
e. Materials and Methods
f. Results
g. Discussion
h. Summary
i. Appendix
j. Literature Cited

A detailed description of the traditional format can be found in the booklet entitled "Instructions for Preparation & Submission of Theses, Dissertations and Dissertation Abstracts". The booklet can be downloaded from the GSBS website.

**FINAL ORAL EXAMINATION**

When the supervising committee judges the dissertation to be suitable for defense, the supervising professor shall submit a Request for Final Defense & Oral Examination Form (page A-9) signed by all committee members (except the outside member) to the Chair of COGS for her/his signature. The signed request form, together with 3 copies of the abstract and the student’s curriculum vita, must be submitted to the office of the GSBS at least two weeks prior to the scheduled date of the final oral examination. In addition, one copy of the entire dissertation should be submitted to the GSBS for the formatting to be checked.

The GSBS makes the public announcement of the final oral examination. However, it is the responsibility of the candidate and the supervising professor to inform the faculty and students of the Department of Pharmacology of the final oral examination.

All interested persons may attend the public defense and have the right to question the candidate. After the public defense, the final oral examination continues with an oral examination by the supervising committee. The supervising committee conducts the final oral examination with the supervising professor serving as the chair. This portion of the examination is restricted to the members of the student's supervising committee. The members of the supervising committee vote on the candidate's success or failure.
on the final oral examination. More than one vote for failure signifies failure of the examination.

The supervising professor submits the Report on Final Oral Examination Form (page A-10) to COGS for approval or disapproval of the recommendation by the supervising committee. In the event of a failing performance by the candidate, the supervising professor and supervising committee will submit a recommendation to COGS regarding remedial action. COGS shall decide on the recommendation or other action to be taken.

GRANTING OF THE DEGREE

If COGS approves the recommendation of the supervising committee, then the Chair of COGS signs and submits the Report on Final Oral Examination (page A-10) along with the final typed copy of the dissertation, including the Dissertation Approval Page signed by all of the supervising committee members, to the Dean. The Chair of COGS reviews the academic performance of the candidate as well as her/his performance on the final oral examination. The COGS Chair certifies that the candidate has satisfied all of the requirements for the degree of Doctor of Philosophy and recommends to the GFC that the candidate be granted the degree. If the GFC approves the recommendation, then the Dean will notify the President of the Health Science Center that the candidate has fulfilled all requirements of the GSBS for the Ph.D. Upon the candidate's certification by the President, the degree is conferred by the University of Texas System Board of Regents. If the GFC does not approve the recommendation, it will refer the matter to COGS with a recommendation for remedial action.

PROCEDURES FOR DISSERTATION AND THESIS BINDING

Typing and Binding of Dissertation

Departmental staff will not type rough drafts or final copies of the dissertation or curriculum vita. Completion of these tasks is the responsibility of the student.

The following copies of the dissertation are required:

- 2 copies for the Briscoe Library – (1) original copy printed on 100% cotton bond paper with original photographs and (1) print shop copy
- 1 original copy printed on 100% cotton bond paper with original photographs for the student
- 1 print shop copy for the Pharmacology Departmental Library
1 print shop copy for each committee member including the outside member

Paying for the Binding and Microfilming

100% cotton bond paper is provided by the Pharmacology Department. The Department will pay for up to 10 copies of each dissertation/thesis. A print shop requisition will need to be completed and the student will need to take the dissertation to the print shop for copying.

The Briscoe Library pays for the binding of one original on 100% cotton bond paper. The Pharmacology Department will cover the costs of copying the dissertation/thesis. In addition, the Department will pay for the binding of up to 10 copies of the dissertation/thesis (one copy for the Departmental Library, one copy for the Briscoe Library, one copy for each committee member, and one copy for the student). The Pharmacology Department will also pay for the microfilming of the dissertation. Additional copies may be bound at the student’s expense and the student must pay to have the dissertation sent off for binding via certified mail.

The student should go to the Graduate Dean’s Office (Rm. 414A) and get an Inter-Departmental Transfer Voucher listing all of the dissertation copies that the Pharmacology Department will pay for binding and microfilming. The Inter-Departmental Transfer Voucher is then taken to the Graduate Program Coordinator for her/his signature and then the form is returned to the Dean’s Office.

Distribution of the Copies for Binding

After the binding and microfilming fees have been paid, the student delivers the copy to be microfilmed to the Graduate Dean’s Office. Each copy should be placed in a separate, labeled envelope (i.e. Tom Smith / Briscoe Library) and delivered to the binding section of the library located on the second floor across from the computer laboratory.

MASTER OF SCIENCE IN PHARMACOLOGY

The Department of Pharmacology does not offer a Master of Science degree in Pharmacology. However, under special conditions, a student may petition to change academic tracks from Ph.D. to M.S. The student must submit to the Chair of COGS a formal request explaining why it is necessary for her/him to change academic tracks. If the request is approved by COGS, the student’s petition is then forwarded to the Graduate Dean’s office for approval.
The MS degree is granted upon satisfactory completion of a minimum of 30 semester hours, additional requirements as determined by COGS, recommendation of the GFC and certification of the candidate by the Dean and President to the Board of Regents.

Master of Science Thesis Requirements

Thesis Supervising Professor

After the student’s change of academic program is approved, the student must choose a supervising professor for her/his thesis research. The student should petition COGS in writing for approval of his/her thesis supervisor. The faculty member must be a member of the Pharmacology graduate faculty, have an active research program, be willing to serve as the student’s thesis supervisor and must have funds to support the student for the entire time required to complete the thesis research project. A student may not select a faculty member who does not have research funds to provide stipend support for the student.

Draft of the Thesis Research Proposal

The candidate shall submit a draft of a proposal for the thesis research to the supervising professor for review and modification. Subsequent drafts of the proposal may then be submitted for review and modification to other faculty members who have knowledge and expertise in the area of the research proposal. After approval of the final proposal draft by the supervising professor, the proposal is submitted to the Committee on Graduate Studies for consideration of approval.

Appointment of the Supervising Committee

Once the student’s thesis proposal is approved by COGS, the supervising professor and the candidate make recommendations to COGS regarding the composition of the Supervising Committee for the thesis research. The Supervising Committee must consist of four people (the supervising professor, two members from the Pharmacology Graduate Faculty, and one member from UTHSCSA who is not a member of the Pharmacology Graduate Faculty). The supervising professor is designated as Supervising Professor and Chair of the Supervising Committee. The Supervising Professor will convene the Supervising Committee as necessary to discuss the progress of the thesis research and the projected future work with the candidate. The Supervising Committee must be fully informed of the research progress and be able to provide continued supervision throughout. COGS should receive reports of the research progress from the Supervising Committee after each of its meetings with the candidate. It will be the Supervising Committee’s responsibility to guide the candidate through the thesis research and certify to COGS that the candidate has carried out a research investigation of the caliber appropriate for a M.S. thesis and has defended it satisfactorily.
Upon selection of the Supervising Committee, the Chair of COGS will submit a completed Form 42 Composition of Supervising Committee – The Master of Science Degree to the Graduate School Dean’s Office. A copy of the proposed work must accompany the form. Each member of the Supervising Committee is required to sign the form to certify her/his approval to serve on the committee.

Registration for Thesis

Students on the M.S. degree track may register for the Thesis course (PHAR 6098) after the following actions have been taken:
- Approval of admission to candidacy for the M.S. degree by the Associate Dean
- Approval of the thesis research proposal by COGS
- Appointment of a Supervising Committee for the thesis research by COGS

A candidate for the M.S. degree must register for one semester of thesis.

Final Credit Hours

A student must be registered for the semester or Summer session in which s/he graduates. If a student is registering only for final credit hours in preparation of a thesis and registers for no other courses, s/he is exempt from the minimum tuition requirement and pays tuition based upon the number of credit hours for which s/he is registered. The minimum number of final credit hours for the M.S. degree is one.

Submission of the Thesis

After members of the Supervising Committee agree that the research has progressed sufficiently for submission of the thesis, the draft of the thesis shall be submitted to the Supervising Professor and the other members of the Supervising Committee as well as the Graduate School Dean’s office for review and recommendation for modification. The candidate should follow the guidelines for preparation of the thesis provided by the Graduate School Dean’s Office in Instructions for Preparation and Submission of Theses, Dissertations and Dissertation Abstracts. If an alternate format appears to be preferable, the candidate must obtain approval to use the alternate format from the Supervising Committee, COGS and the Dean.

Final Oral Examination

The Graduate School requires that the thesis be defended by the candidate in a Final Oral Examination conducted by the Supervising Committee. COGS may choose either of the options below as the format of the Final Oral Examination.
Option 1: COGS may require that the thesis be defended in a formal Final Oral Examination scheduled through the Graduate School Dean’s Office and open to all interested persons. The procedure for arranging this Final Oral Examination is the same as that for the Ph.D.

Option 2: COGS may choose a less formal format that doesn’t entail public notification from the Graduate School Dean’s Office. In this case, the Supervising Committee submits a Request for Final Oral examination Form to the Chair of COGS. If approved, the request then goes to the Graduate School Dean’s Office.

Two copies of the abstract and the Vita should be submitted with the request for the candidate’s files in the Registrar’s Office and the Graduate School Dean’s Office.

The Supervising Committee members vote on the candidate’s success or failure on the Examination; more than one vote for failure signifies failure on the Final Oral Examination. In the event of a failing performance, the Supervising Committee submits the Report on Final Oral Examination to COGS with recommendations regarding remedial action or further examinations. In this situation, COGS will decide what recommendation or other action to follow. If the student’s performance in the Oral Examination is successful, the Supervising Committee submits the same report to the COGS, which then votes on whether to approve the recommendation of the Supervising Committee to grant the MS degree.

Recommendation for Granting of the Degree

Once COGS approves the favorable recommendation by the Supervising Committee, the Chairman of COGS submits the Report on Final Oral Examination to the GFC for consideration. The candidate then submits the final typed copy of the thesis (including the thesis Approval Page signed by the Supervising Committee members) to the Graduate School Dean’s Office. The GFC will consider the recommendation for granting the degree when both the Report and the thesis copy have been received. If the recommendation for granting the degree is not approved, the Council will refer the matter to COGS with a recommendation for remedial action. If the recommendation is approved, the Dean of the Graduate School of Biomedical Sciences will notify the President of the University of Texas Health Science at San Antonio that the candidate has fulfilled the requirements for the degree of Master of Science. Upon the candidate’s certification by the President, the degree is conferred by The University of Texas System Board of Regents.
MISCELLANEOUS INFORMATION

Graduate Teaching/Research Assistantship Stipends

Graduate students who are enrolled full-time and who remain in good academic standing may receive a yearly stipend in the form of a graduate teaching/research assistantship as recommended by COGS to the department Chair. Currently, this stipend is $21,000 for all graduate students, and is guaranteed for five years, provided the student remains in good standing within the Department. The award of a graduate teaching/research assistantship stipend is reviewed annually by the COGS. Students who apply for and receive grant funding (e.g. a National Research Service Award {NRSA}) will be subsidized by the department if the grant funding doesn’t match that of the stipend.

Time to Degree

A minimum of 72 semester credit hours is required for a Ph.D. degree. It is expected that full-time Ph.D. candidates will complete the requirements for the Ph.D. degree within a maximum of six years or within 130 credit hours. If a student is unable to complete the requirements for the degree within this time period, the student and the supervising professor may petition COGS for an extension. COGS will make a determination based upon evidence of adequate progress that would justify an extension. The Pharmacology Department has no obligation to financially support a graduate student for more than six years. In addition, students enrolled for more than 130 credit hours will be required to pay nonresident tuition for all subsequent semesters.

Faculty Mentor

A faculty mentor will be assigned to each first-year graduate student. In subsequent years, the dissertation supervisor serves as the student's academic advisor and dissertation supervisor.

First year students also have a Peer Advisor chosen from the student body.

Student Travel

During their tenure in the graduate program, students will be eligible for a maximum of $750 in State funds to support travel to scientific meetings. This money is to be used within the first two years before a student has selected a lab. At the time a lab is selected, any unused funds go back to the Department and the PI will be responsible for any needed travel funds. Prior to travel, students must petition COGS (in writing) for the
use of such travel funds. Students may use State funds to travel to meetings if they are in good academic standing and are presenting a paper/poster.

**Copying**

All students will be allowed a maximum of $80.00 (4 - $20.00 renewals) for copying from Departmental funds during each of the first two years in the program. Once the student has selected a Supervising Professor and entered a lab, copying costs become the responsibility of the Supervising Professor.

**Distribution of the COGS Meeting Minutes**

Distribution of the minutes of the meetings of the COGS is limited to the Graduate Faculty of the Pharmacology Graduate Program and the Graduate Student Representative.

**Payment for Tutorial Services**

A graduate student may not accept payment for tutorial services rendered to a student if the graduate tutor could potentially be involved in the student's evaluation through lecturing, grading of examinations, review of grades, etc.

If no such potential conflict of interest exists, then the graduate student may tutor students for remuneration provided the graduate student first informs the tutee of the fee to be charged for the service.

**Proctoring of Examinations**

As part of their teaching assistantship responsibilities, graduate students may be asked to help the faculty proctor examinations in various Medical and Dental Pharmacology courses.
COURSE DESCRIPTIONS

REQUIRED COURSES

**CSBL 5095** - Experimental Design and Data Analysis (2 credits)

Course Director: Dr. Morgan

The purpose of the course is to provide an introduction to experimental design and statistical analysis. The emphasis of the course will be on the selection and application of proper tests of statistical significance. Practical experience will be provided in the use of both parametric and nonparametric methods of statistical evaluation. Among the topics to be covered are: data reduction, types of distributions, hypothesis testing, scales of measurement, chi square analysis, the special case of the comparison of two groups, analysis of variance, a posteriori multiple range tests, tests of the assumptions of parametric analyses, advanced forms of the analysis of variance, linear regression and correlation analysis.

**INTD 5005** – Core Course I: Biochemistry  (4 credits)

Course Director: Dr. McAlister-Henn

A survey of the field of biochemistry designed for graduate students, covering such areas as protein structure, enzymology, the metabolism and chemistry of carbohydrates, lipids, amino acids and nucleotides as well as the synthesis and function of macromolecules.

**INTD 5006** – Core Course II: Molecular Biology (4 credits)

Course Director: Drs. Kolodrubetz and Kraig

This course is a study of the molecular aspects of prokaryotic and eukaryotic genome structure and expression. Lectures will examine the current understanding of gene organization, regulation of transcription, RNA structure and function, translation and replication.

**INTD 5007** – Core Course III: Cellular Biology (4 credits)

Course Director: Dr. Sun

This course offers students the opportunity to gain the fundamentals of molecular cell biology necessary to read, understand and evaluate the current research on each of the topics covered. The topics include: plasma membrane, intracellular sorting, nucleus-
chromatin, energy conversion, cytoskeleton movements, cell signaling, cell growth and division, cell adhesion and extracellular matrix meiosis, germ cells/fertilization and social behavior of cells.

**INTD 6002 - Ethics in Research (0.5 credits)**

Course Director: Dr. Baseman  
Spring

All second-year graduate students are required by the Graduate School to take this course or its equivalent.

This course will deal with topics relevant to ethics in scientific research. The course will be taught on a ‘case study’ basis, dealing with real and hypothetical situations relevant to the conduct of scientific research. Topics discussed will include, but will not be limited to: data management, peer review, recognizing scientific misconduct, authorship and The University of Texas regulations relevant to human and animal research.

**PHAR 5001 – Pharmacology (4 credits)**

Course Director: Dr. Mifflin  
Spring

The course begins with basic pharmacologic principles applicable to all drugs. The remainder of the course addresses major drug classes that are discussed using prototype drugs. Drugs, which are exceptions to, or variations from, prototypes, are emphasized. The course emphasizes drug therapeutics, side effects, toxicity, precautions, contraindications and interactions that have particular relevance to dentistry. How knowledge of basic pharmacology can be used to assess drug manufacturers’ claims is illustrated by analyzing published drug advertisements.

**PHAR 5013 - Principles of Pharmacology (3 Credits)**

Course Director: Dr. Clarke  
Fall

Principles of drug action; receptor classification and quantitation; dose-response relationships; cellular mechanisms of drug action; fundamental concepts of drug-receptor interactions; voltage-gated and ligand-gated ion channels; drug actions mediated by transduction and non-transduction enzymes; time course of drug action; absorption, distribution, biotransformation and elimination of drugs; pharmacokinetics; experimental approaches to drug action.
PHAR 5020 - Basics of Research Design (1.5 credits)    Summer

Course Director: Dr. Giuffrida

The course aims at teaching first year graduate students fundamentals of research design and analysis of scientific literature to orient them with setting up scientific experiments and writing grant proposals. The course is divided in 3 sections:

- **Research Design**: students are thought how to choose testable hypotheses, design an experiment and control variables.
- **Communicating scientific data**: provides guidelines for communicating scientific data, writing a manuscript and reviewing scientific papers.
- **Getting scientific ideas funded**: provides guidelines for the preparation of grant proposals.

PHAR 5090 - Pharmacology Seminar (1 credit)

Course Director: Dr. France    Fall/Spring/Summer

Presentation and discussion of recent advances and research by staff, students, and outside scientists.

Each graduate student is expected to register for Seminar each Fall or Spring semester the student is enrolled in graduate school. If a student is registered for nine (9) or more credit hours, the student need not register for Seminar hours.

All students are required to attend each departmental Seminar and Journal Club each semester s/he is enrolled in graduate school regardless of whether or not s/he is registered for Seminar. Students may be required to sign in at each seminar in order to record her/his attendance. Receiving two or more unexcused absences at Seminar or Journal Club will result in the loss of travel funds and/or the student receiving a grade of ‘Unsatisfactory’ for the course. Possible consequences of receiving a grade of ‘Unsatisfactory’ for Seminar include, but are not limited to the following: 1) the Department could terminate the student’s departmental funding; 2) student may be referred to the Chair of the Department for appropriate action; 3) student may be dismissed from the program. In addition, a student must petition COGS in writing if s/he would like for an absence to be excused.

PHAR 5092 - Special Problems in Pharmacology (1 credit)

Course Director: Dr. France    Fall/Spring/Summer

Students must complete two laboratory rotations in different laboratories by the end of the first year in the graduate program. Laboratory rotation mentors may be selected
from the Graduate Faculty of the Pharmacology graduate program who have active research laboratories. Each rotation is a full-semester rotation. Students are expected to work at least 12 hours per week in their laboratory rotations during the Fall and Spring semesters and to work full-time in the laboratory in the Summer session. Students present a 15 minute post-laboratory rotation talk following completion of each laboratory rotation. Students are encouraged to contact their Special Problems supervisor who will assist them in the preparation and organization of the oral presentation.

Students are expected to register for Pre-dissertation Research hours following completion of the second Special Problems Laboratory Rotation. A student may request permission to pursue a third Special Problems Laboratory Rotation, but may not register for more than 3 semesters of Special Problems.

**PHAR 6071 - Supervised Teaching** (credit to be arranged)

Course Director: Dr. France Fall/Spring/Summer

The Graduate School requires that all graduate students register for supervised teaching. A student should register for this course upon registering for his/her first lab rotation. The requirement will be fulfilled through presentations of lab rotation data, Journal Club presentations, the oral Qualifying Exam, and the Dissertation proposal and defense. If a student wishes to have a more formal Supervised Teaching experience, opportunities might be available to lecture in the Dental Hygiene Pharmacology course under the supervision of the Course Director.

**PHAR 6097 – Research** (credit to be arranged)

Course Director: Student’s Faculty Advisor Fall/Spring/Summer

Independent, original research under the direction of a faculty advisor. Following admission to candidacy, students register for research hours to maintain full-time student status.

**PHAR 6098 – Thesis: MS Students** (credit to be arranged)

Course Director: Student’s Faculty Advisor Fall/Spring/Summer

Prerequisite: Admission to candidacy for the MS degree; approval of thesis research proposal by COGS; and appointment of a Supervising Committee for the thesis research by COGS
Registration for at least one term is a Graduate School requirement for all MS candidates.

**PHAR 7099 – Dissertation: PhD Students (credit to be arranged)**

Course Director: Student’s Faculty Advisor  
Fall/Spring/Summer

Prerequisite: Admission to candidacy for Doctor of Philosophy degree; approval of dissertation research proposal by COGS, GFC and the Dean; and approval by GFC and the Dean of the Supervising Committee for the dissertation research recommended by COGS.

A student must register for at least two semesters of Dissertation prior to the anticipated graduation date, but there is no required number of credit hours for Dissertation.

**Special Topics: Orientation to Pharm. Graduate Studies** (0 credits)  
Fall

Course Director: Dr. Clarke

This course will provide students with direction as to what is expected of them in graduate school. Additionally, it will assist students in maximizing their chances for success as research scientists. The class will meet on Mondays immediately following Principles of Pharmacology (11:30 – 12:00) in the Department’s conference room.

**Special Topics: Introduction to Lab Rotations** (0 credits)  
Fall

Course Director: Dr. Clarke

The purpose of this course is to provide a means by which the faculty can communicate their research interests to the students. By acquainting the students with the faculty and their research, the students will be able to more easily choose laboratories in which to do rotations. This class will meet on Wednesdays and Fridays after Principles of Pharmacology (11:30 – 12:00) in the conference room.
ELECTIVE COURSES

BIOC 6033 - Cell Signaling Mechanisms (2 credits)

Course Director: Dr. Jiang        Spring

This course covers the molecular mechanisms of action of various extracellular mediators including hormones, neurotransmitters, growth factors, cytokines, etc. and cell signaling events. Several areas will be discussed including (1) mechanisms of mediator synthesis, (2) interaction of mediators with specific receptors, (3) modulation by mediators of various second messenger systems including cyclic nucleotides, inositol phospholipids, calcium, protein phosphorylation, ion flux, etc. and (4) intra- and intercellular mechanism for regulating mediator action.

CSBL 6048 – Molecular Biology of Aging (3 credits)    Fall

Course Director: Dr. Smith

The purpose of this course is to provide students with the most up-to-date information on the current understanding of the aging process. This advanced interdisciplinary graduate course will be offered to students who wish to either specialize in or have a strong background in the interrelated areas of aging and age-related diseases. Faculty from the Departments of Cellular & Structural Biology, Physiology, Pharmacology and Medicine will be involved in teaching this course, which will cover the molecular and cell biology of aging, model systems used for aging studies, age related changes in organs and tissues and age related diseases. This course is an elective for all Departments.

INTD 5040 – Fundamentals of Neuroscience I: Molecular, Cellular, & Developmental Neuroscience (4 credits)

Course Director: Dr. Roberts        Fall

This course is intended to introduce students to a broad survey of the basics of molecular, cellular, and developmental neuroscience. The course is organized into a series of three modules: 1) Biochemical & Cellular Properties of Nervous System Cells; 2) Development of Neuronal Systems; and 3) Neurotransmission & Neuromodulation. Current topics and concepts are discussed in Discussion Sessions, which include student participation.
INTD 5043 – Fundamentals of Neuroscience II: Systems Neuroscience (4 credits)

Course Director: Dr. Morilak       Spring

This course, the second component of our broad survey of the basics of neuroscience, begins at the level of the neural circuit, and guides the student through an understanding of increasingly complex levels of organization and function in the brain. Topics include neurotransmitter systems, sensory and motor function, motivated behavior, regulation and integration of autonomic, behavioral and emotional responses in the limbic system, higher order cognitive processes, and the neurobiological basis underlying some important psychiatric disorders and their treatment.

INTD 5047 – Neuroanatomy (3 credits)

Course Director: Dr. Vaughan       Spring

An interdisciplinary introductory course representing a subset of lectures, labs, and case conferences, all focusing on neuroanatomy, derived from the Medical Neuroscience course directed by Dr. Mary Vaughan. Lecture and lab topics include Gross Neuroanatomy, Neurocytology, Cerebral Circulation, Blood-Brain Barrier, Neurodevelopment, Sensory Receptors, Spinal Reflexes, Cerebellum, Basal Ganglia, and Motor Systems.

INTD 6041 – Basic Science Resident Lecture Series in Neurology (1.5 credits)

Course Director: Dr. Carolin       Fall/Spring

An interdisciplinary advanced elective in which students attend 20 lectures, selected from the full offering of daily one-hour lectures comprising the Neurology Residents’ Basic Sciences lecture series. These lectures cover a range of topics, such as Epilepsy, Movement Disorders, the Thalamus, Parkinson’s Disease, Alzheimer’s Disease, Stroke, Sleep, etc., all given from a clinical perspective. In addition, graduate students will have the opportunity to observe or participate in at least two enrichment activities related topically to the lectures they attend, which may include such settings as case presentations, diagnostic training sessions, or clinical observation sessions, again selected from the list of offerings in the Neurology Residents’ series.

PHAR 5091 - Micro-electives (1 credit)

Course Director: Dr. France       Fall/Spring/Summer

Micro-electives are courses, which can be of any type ("tutorial" or original literature review, short (2 week) didactic, technique, etc). Complete course descriptions can be
found on the Department of Pharmacology's web site. The terms in which the courses are offered may vary. Check the online list of courses each term to determine the offerings.

5091.001 New Views on Monoaminergic Neurotransmission: Are Transporters Important?  
Course Director: Daws

5091.002 Ion Channelopathies in Neurological Disease  
Course Director: Sanchez

5091.003 Historical Perspectives of Receptor Theory  
Course Director: Clarke

5091.004 Cell Membrane Microdomains and Signaling  
Course Director: Clarke

5091.005 Neuropeptide Metabolism  
Course Director: Roberts

5091.006 Serotonin: From Soup (Transmission) to Nuts (Behavior)  
Course Directors: Frazer & Hensler

5091.007 Course no longer offered.

5091.008 Neural Substrates of Regulatory Behaviors: Peptides and Monoamines  
Course Director: Cunningham

5091.009 Current Issues in Basic Research on Mechanisms of Epilepsy  
Course Directors: Cavazos, Brenner, & Sanchez

5091.010 Appetite Control: Adiposity Hormones and Neuropeptides  
Course Director: Lu

**PHAR 6020** – Molecular & Pharmacological Basis of Therapeutics (2 credits) Fall

Course Director: Dr. Lam

This course provides graduate students with current knowledge of how genetic variants can affect drug response and the potential to optimize drug therapy. Course format will include lectures, discussion of selected literature, individual student presentations, and development of a mini pharmacogenetic/genomic protocol and consent form to address a clinical/biomedical question mutually agree upon between course director and students.
**PHAR 6025 - Molecular Pharmacology (2 Credits)**

Course Director: Dr. Liu

Spring

This course is presented in a journal club/paper discussion format and will focus on the molecular aspects of pharmacology, with emphasis on molecular biology, biochemistry, and cell biology of a variety of physiological systems subjected to pharmacological manipulation. The topics to be discussed will include molecular mechanisms of drug action, signal transduction and regulation, molecular approaches and recent advances in various areas of molecular pharmacology.
THE FACULTY AND THEIR RESEARCH INTERESTS

THE DEPARTMENT OF PHARMACOLOGY THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT SAN ANTONIO

Revised August 2006
José E. Cavazos, M.D., Ph.D.
Assistant Professor of Medicine (Neurology) and Pharmacology

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My laboratory studies activity-dependent plasticity in the hippocampal formation in the developing, adult, and aged brain using a variety of experimental models of epilepsy, seizures, and epileptogenesis. Previous studies from my laboratory have shown that repeated seizures induce progressive neuronal death and axon sprouting that permanently alter the hippocampal circuitry lending it more susceptible to additional seizures and memory dysfunction. We currently are investigating the molecular mechanisms that link the synchronous neuronal hyperexcitability with these morphological events including the role of caspases using in-vivo models and in-vitro organotypic hippocampal slice cultures. We investigate the features of seizure-induced axon sprouting in other limbic circuitries using anatomical tracing techniques, and their electrophysiological consequences in the neuronal excitability of the abnormally connected circuitry using brain slices. Lastly, we are evaluating several antagonists at the various steps in this cascade that leads to circuit plasticity with the aim of identifying the crucial steps in the epileptogenic process amenable to novel pharmacological targets for a better treatment of seizures and epilepsy.

Selected Publications


Work in my lab centers on questions concerning the molecular nature of drug efficacy and the cellular mechanisms by which efficacy can be regulated. An understanding of the nature of drug efficacy and the factors by which it is regulated is essential for the design of rational treatment regimens in clinical situations. Drug efficacy is defined as the ability of a drug to produce a response. According to traditional receptor theory (see equation #1), the magnitude of an effect (E) produced when an agonist at a specified concentration ([A]) interacts with a receptor is a function (f) of the stimulus (S) produced by the agonist and depends upon 4 factors. Two of these are chemical properties of the agonist itself unique for each ligand-receptor pair; the affinity related parameter, $K_A$, and "intrinsic efficacy" $\varepsilon$ ($\varepsilon$ describes the capacity of a drug to produce a receptor "stimulus" {which can be thought of as a conformational change in the receptor} which is transmitted to the signal transduction components of the cell). The remaining two parameters are cell or tissue dependent properties; receptor density, $R_T$ and a function, $f$, that describes the efficiency of signal transduction. Thus, cellular mechanisms that influence drug efficacy are those that regulate any or all of these four parameters.

$$E = f(S) = f\left(\frac{\varepsilon_A \cdot R_T}{1 + \frac{K_A}{[A]}}\right)$$

Equation #1

The drug property, intrinsic efficacy, according to traditional receptor theory, is a unique for each drug-receptor pair and is independent of the response measured. Thus, if a drug produced a 50% response (relative to that of a reference drug) for one measure, it must also produce a 50% response for all measures coupled to a receptor. Recent evidence from our laboratory, and others, challenges that assertion. Work in our lab has centered upon understanding the mechanisms by which drug intrinsic efficacy is response-dependent. Our working hypothesis is that drugs can elicit unique spectra of receptor conformations that have differential capacities to activate signaling mechanisms in cells.

Current models of receptor function are based on the existence of receptors in equilibrium between multiple conformations or states that display differential degrees of activity toward cellular signaling mechanisms in the absence of a ligand. One consequence of which is that receptors can activate signaling mechanisms in cells in the absence of a ligand (constitutive receptor activity) and some drugs have the capacity to turn off, as well as turn on, receptors. Drugs that reduce constitutive receptor activity are called inverse agonists and are said to have negative intrinsic efficacy. Work
in our lab has been devoted to understanding the physiological and pharmacological consequences of inverse agonism and how it can be regulated.

Cellular factors involved in the regulation of drug efficacy that are under investigation include the consequences of activation of other receptor systems on cells (so-called "cross-talk" between receptor systems) and mechanisms of desensitization (homologous and heterologous). Furthermore, the impact of subcellular localization of receptors and signaling molecules with respect to membrane microdomains on drug efficacy is also under study.

**Selected Publications**


Berg KA, Clarke WP. Regulation of 5-HT(1A) and 5-HT(1B) receptor systems by phospholipid signaling cascades. Brain Res Bull. 2001 Nov 15;56(5):471-7. Review.


**Tom Cunningham**  
Associate Professor of Pharmacology  
Ph.D., University of Iowa  
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We study the role of the central nervous system in body fluid homeostasis and blood pressure regulation. Specifically we are interested in the integration of hormonal factors such as circulating angiotensin and neural input from baroreceptors and volume receptors and how this interaction might influence vasopressin release, sympathetic outflow, and the ingestion of fluid and salt. To pursue this type of research we employ
an integrative approach that includes in vivo electrophysiology, immunocytochemistry, neuroanatomical tract tracing and measuring salt and water intake. Our current research focuses on using neurophysiological approaches to investigate central pathways that are stimulated by volume expansion and how these systems are influenced by exposure to microgravity or cardiovascular deconditioning. Other studies focus on the role of AP-1 transcription factors in the regulation of hypothalamic neurosecretory cells. Research of this nature cannot only provide information on central nervous function, but also demonstrate how behavioral and physiology regulatory mechanisms are organized and integrated to maintain homeostasis. Furthermore, describing the role of the central nervous system in homeostasis is also likely to reveal how disturbances in these systems can produce pathological states, such as hypertension.

Selected Publications


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**Lynette C. Daws**  
**Assistant Professor of Psychiatry**  
**Ph.D. Flinders University of South Australia, Australia**

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E-mail: daws@uthscsa.edu

The broad area of my research is studying the function and regulation of biogenic amine transporters (the serotonin, dopamine and norepinephrine transporters). Understanding how these transporters function is important in that they are the primary site of action for numerous psychotherapeutic and psychoactive drugs and are pivotal in controlling the extracellular concentration of biogenic amines and hence, neurotransmission. One of my primary research interests relates to the serotonin transporter. In humans, a polymorphism of the gene encoding the serotonin transporter leads to its reduced expression. This polymorphism has been linked to a number of disorders including alcoholism and depression. Moreover, individuals with this polymorphism appear to respond differently to drug treatment. We are using mice with a genetically induced reduction in the density of the serotonin transporter (heterozygote serotonin transporter knockout mice, which express 50% fewer serotonin transporters than the “normal”, wild-type mouse) to investigate neuroadaptive changes associated with reduced expression of the transporter. In particular, we are interested in studying if regulation of the serotonin transporter by the 5-HT\textsubscript{1B} autoreceptor is altered in these mice.

My group is also interested in studying how drugs of abuse interact with biogenic amine transporters. We are currently investigating the mechanism of action of MDMA
("Ecstasy"), para-methoxyamphetamine and cocaine at these transporters, as well as the acute and long term effects of these drugs on transporter function in vivo. In addition, we are studying the effect of acute and chronic alcohol consumption on a number of serotonergic parameters (e.g. 5-HT1B and 5-HT3 receptor density; 5-HT uptake) as it relates to genetic variation in transporter expression. My current research implements several state-of-the-art techniques including high-speed chronoamperometry and quantitative autoradiography, as well as a variety of molecular and behavioral approaches. My research group comprises Drs. Lora Talley Watts and Nina Koldzic-Zivanovic (Postdoctoral Fellows), W. Anthony Owens (Senior Research Assistant), Jaclyn Munn and Rebecca Horton (Research Assistants), Nicole Baganz (Graduate Student), and Adrian France & Julianne Doyen (Summer Research Students).

Selected Publications


Lily Q. Dong
Assistant Professor of Cellular and Structural Biology
Ph.D., Iowa State University
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Insulin resistance is a primary contributing factor in the pathogenesis of type 2 diabetes. This condition is characterized by the loss of insulin sensitivity in tissue, resulting in an impairment of glucose breakdown in cells, an unregulated production of glucose in hepatic cells, and a reduction of glucose uptake in skeletal muscle, resulting in a greatly increased glucose level in the bloodstream.

Recent studies have identified a new hormone in the human body known as adiponectin or Acrp30. Adiponectin/Acrp30 is secreted by adipose tissue and is released into the bloodstream. The serum concentration of adiponectin has been found to be significantly reduced in type 2 diabetic and obese patients. Adiponectin/Acrp30 has been shown to enhance insulin sensitivity by promoting glucose uptake and increasing fatty acid oxidation. Adiponectin/Acrp30 has also been found to prevent the growth of blood vessels supplying adipose tissue. However, the molecular mechanism governing adiponectin/Acrp30 action is largely unknown.

Our current research interest is focused on the elucidation of the molecular pathway(s) mediating adiponectin signaling in cells, and the investigation of the molecular
mechanism regulating adiponectin levels in the human body. As adiponectin plays a
protective roles in the prevention of insulin resistance and antiangiogenesis, it has the
potential to be used therapeutically in the treatment of type 2 diabetes and obesity, and
the findings from our studies will shed light into the mechanisms behind insulin
resistance and the development of type 2 diabetes.

Selected Publications

(Publications before 1997 were under the name of Dong, Q.)

Mao, X., Hong, J.Y., and Dong, L.Q. (2006). The adiponectin signaling pathway as a
novel pharmacological target. Mini Reviews in Medicinal Chemistry. (in press).


Dong, L.Q. (2006). APPL1 bonds to adiponectin receptors and mediates adiponectin

stimulated degradation of the insulin receptor: a mechanism of negative regulation. Am
J Physiol Endocrinol Metab., 290, E1262-E1266.

master kinase in the cytosol? J Cell Biochem., 96, 1157-1162.

Phosphorylation Sites Using Mass Spectrometry Analysis: Regulatory Role of Serine
1223. Endocrinology, 146, 4410-4416.

Phosphorylation of Grb10 by Mitogen-Activated Protein Kinase: Identification of Ser150
and Ser476 of human Grb10zeta as Major Phosphorylation Sites. Biochemistry, 44,
8890-8897.


1 and PKN in regulating cell migration and cortical actin formation of PTEN-deficient
cells. Oncogene, 23, 9348-9358.

Negative regulation of insulin-stimulated MAP kinase signaling by Grb10. Mol. Endo, 18,
350-358.

Charles France
Professor of Pharmacology
Ph.D., University of Michigan

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Research in my laboratory focuses on interactions between behavior and pharmacology as those interactions influence the abuse liability of drugs. One major goal of the laboratory has been to understand how the subjective effects of drugs change as a consequence of certain behavioral and pharmacologic histories. This laboratory has developed behavioral procedures (drug discrimination) that are sensitive to the withdrawal-precipitating effects of antagonists and we use these procedures to study the development of dependence and the expression of withdrawal as well as how these phenomena can be modified by various pharmacologic and behavioral manipulations.

One unifying theme of research in this laboratory is the use of receptor theory, which provides a framework for the planning, execution and interpretation of behavioral studies with drugs. Thus, many of our studies attempt to differentiate among drugs on the basis of their efficacy and selectivity, thereby identifying the pharmacologic characteristics of drugs that are most important for particular behavioral effects (e.g., reinforcing effects).

Current areas of research include the following: studies on the mechanism of action, abuse and dependence liability of GHB and related "club drugs"; the role of insulin receptor pathways in regulating dopamine transporter activity and sensitivity to stimulants; GABA receptor heterogeneity and the dependence liability of sedative/hypnotics; and the influence of physical dependence on the reinforcing effects of opioids.

Selected Recent Publications


McMahon, L.R., & France, C.P. (2003) Discriminative stimulus effects of positive GABA_A modulators and other anxiolytics, sedatives, and anticonvulsants in untreated


Alan Frazer  
Professor of Pharmacology and Psychiatry  
Chair of Pharmacology  
Ph.D., University of Pennsylvania

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My primary research interest is the mechanisms of action of antidepressants. Most often, an in vivo approach is taken whereby measurements are made of effects produced by various types of antidepressants on noradrenergic or serotonergic neurons, on neurochemical or behavioral responses elicited by these neurotransmitters, or on their receptors. Neuroanatomical localization of drug-induced effects is emphasized by employing techniques such as quantitative autoradiography, immunohistochemistry, and in vivo voltammetry. Most of our recent work has used the latter technique to measure the rate of clearance of serotonin from extracellular fluid (ECF) in discrete regions of rat brain. Our lab is one of the few in this country that uses this technique to do this.

The clearance of serotonin is primarily a reflection of the functioning of the serotonin transporter (SERT), a membrane protein that is a key target for drugs such as fluoxetine (Prozac). Our results demonstrate differences in the biogenic amine transporters responsible for the clearance of serotonin in different regions of brain. We also found that SERT function is desensitized upon chronic treatment of rats with selective serotonin reuptake inhibitors (SSRIs) such as sertraline (Zoloft) or paroxetine (Paxil). This downregulation had a significantly greater inhibitory effect on the clearance of serotonin from extracellular fluid than acute blockade of the SERT with SSRIs. Importantly, it took about 10-15 days for such downregulation to occur, a time when behavioral improvement that these drugs cause in depressed patients becomes
recognizable. Selective norepinephrine reuptake inhibitors, such as the antidepressant desipramine, produce a downregulation of the norepinephrine transporter (NET), but do not cause this effect on the SERT. We have begun recently to study cognitive and emotional behaviors in animal "models" of depression to begin to integrate psychological theories of depression with biological processes in brain affecting relevant behaviors and antidepressant effects.

Research Associates

The research in my laboratory is currently being carried out by Dr. Saloua Benmansour (Research Instructor), Dr. Georgianna Gould (Postdoctoral Fellow), and Jonathan Piotrowski (Research Assistant).

Societal Affiliations

Dr. Frazer is a member of numerous societies including the American Society of Pharmacology and Experimental Therapeutics, the American College of Neuropsychopharmacology, the Collegium Internationale Neuro-Psycho-pharmacologicum, and the Society of Neuroscience. He has been awarded a Merit Award from NIH and has been a Career Scientist of the Department of Veterans Affairs. In addition to serving on the editorial boards of several journals, he is currently the field editor for preclinical neuropsychopharmacology of the International Journal of Neuropsychopharmacology.

Selected Publications


Andrea Giuffrida
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My laboratory is interested in the role played by the endogenous cannabinoid system in regulating psychomotor functions. The endocannabinoids are a family of naturally occurring lipids that mimic the effects of marijuana by stimulating specific receptors expressed in the brain (cannabinoid receptors). CB1 cannabinoid receptors are particularly abundant in areas of the central nervous system that are critical for the regulation and planning of motor behaviors, such as the basal ganglia. Furthermore, the endocannabinoid anandamide may serve as an inhibitory feedback signal countering dopamine-induced motor activation. Thus, the endocannabinoid system represents a new pharmacological target for the treatment of diseases characterized by a dysregulation of dopamine transmission, such as Parkinson's disease and schizophrenia.

We integrate neurochemistry and behavioral pharmacology to study how endocannabinoids regulate the interplay of activities of different neurotransmitters in the basal ganglia and how disturbances in endocannabinoid transmission contribute to psychomotor disorders, such as Parkinson's disease, essential tremor, schizophrenia and drug-induced dyskinesias.

Our laboratory is also interested in: 1) the neuroprotective effects of cannabinoid drugs in animal models of Parkinson's disease; 2) implantation of tissue-engineered constructs to repair the nigro-striatal pathway in Parkinson's disease.

Selected Recent Publications


Ken M. Hargreaves  
Professor and Chair, Endodontics; Professor of Pharmacology  
D.D.S. Georgetown University  
Ph.D., Uniformed Services University of the Health Sciences  
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My primary research interests are in the pharmacology of pain and inflammation. A major focus is on pharmacological regulation of unmyelinated "C" fiber nociceptors, as well as their plasticity in response to inflammation or nerve injury. Investigations are in progress evaluating the effects of cannabinoids, opioids, adrenergics, NPY, sex steroids and other drugs on regulating the activity of these fibers. In addition, we are interested in identifying major classes of inflammatory mediators and associated receptor/signal transduction systems which mediate activation, sensitization and phenotypic plasticity of these primary afferent fibers in response to tissue inflammation. Responses are measured using isolated superfused tissue, primary trigeminal cultures, microdialysis probes implanted in situ, RIA, EIA, real time PCR, Affymetrex analyses, IHC, ISH, confocal microscopy, behavior, etc.

Selected Publications


George Henderson  
Professor of Medicine and Pharmacology  
Ph.D., Vanderbilt University  

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E-mail: hendersong@uthscsa.edu  

The primary objective of my research is to gain a better understanding of the basic mechanisms underlying alcohol and oxidative stress-induced damage to the developing brain. The pro-oxidant effects of ethanol have been documented in adult and fetal tissues (brain and liver) using in vivo models and in primary cultures of fetal rat cortical neurons and neonatal rat cortical astrocytes. Current studies are focusing on the accelerated apoptotic death of neurons exposed to alcohol with mitochondria as the source of reactive oxygen species and astrocyte-mediated protection from this apoptotic death. Findings in our laboratory have illustrated that the well-documented increase in neuron death in the ethanol-exposed developing brain may be due to enhanced mitochondrially-mediated apoptosis. Confocal and multiphoton imaging of live fetal cortical neurons have illustrated that ethanol can elicit an increase in reactive oxygen species within only minutes of exposure and that this is associated with decreased levels of the antioxidant, glutathione. This is rapidly followed by production of toxic aldehyde products of lipid peroxidation that have strong proapoptotic properties. These reactive compounds form inhibitory adducts with key cellular proteins, such as cytochrome c oxidase of the respiratory chain. Additionally, in the fetal brain, catalase-mediated oxidation of ethanol produces elevated levels of another toxic aldehyde, acetaldehyde, which likewise forms tissue adducts. Both of these settings are being explored as possible mechanisms underlying neurotoxic responses to ethanol. In summary, current studies address oxidative stress-mediated apoptotic neuron death in the developing brain, the role of glutathione antioxidant systems in protection against this, and the means by which astrocytes protect neurons from ethanol-mediated damage.

Selected Publications


Because the treatment of many psychiatric disorders involves long term pharmacological intervention, I am interested in the molecular mechanisms by which neurotransmitter receptor systems compensate (or regulate) following drug treatment. Compensatory changes of central receptor systems may be involved in the mechanism by which psychotropic drugs produce their therapeutic or side effects. My research group has focused primarily on the regulation of serotonin receptor function. The serotonergic system in brain has been implicated in substance abuse and addiction, as well as many psychiatric disorders. We have used both in vivo and in vitro approaches to examine the processes by which serotonin receptor function is regulated in disease states such as alcoholism, or following long-term treatment with drugs used to treat mental illness. In vivo studies have included the investigation of regulatory interactions between serotonin-1A (5-HT$_{1A}$) and serotonin-2 (5-HT$_{2}$) receptors. We are currently interested in how the serotonergic and noradrenergic systems interact to modulate the regulation of the 5-HT$_{1A}$ receptor. We have also begun studies to identify differences in serotonin receptors and in the serotonin transporter in genetically modified mice, which may prove useful models in which to examine the role of the serotonin system in alcohol and drug abuse. For example, we are interested in examining in mice deficient in brain-derived neurotrophic factor (BDNF) the neurochemical and behavioral effects of decreases in BDNF expression, as well as neurobiological changes in the serotonergic system that underlie alcohol preference and aggression. 5-HT$_{1A}$ receptor function at the level of receptor-G protein interaction, is measured following chronic drug treatment using $[^{35}\text{S}]$GTPyS autoradiography. In vitro systems, (i.e. cells in culture), allow us to examine the regulation of serotonin receptors in more mechanistic studies; our findings from these studies are compared to brain. Cell lines, which have been transfected to express various serotonin receptor subtypes, as well as cell lines which endogenously express these receptors, are used.

**Selected Publications**

Advani, T., Hensler, J.G., and Koek, W. Effect of early rearing conditions on alcohol drinking and 5-HT$_{1A}$ receptor function in C57BL/6 mice. Int. J. Neupyschopharmacol. (accepted)


Hensler J.G.: Regulation of 5-HT1A receptor function in brain following agonist or antidepressant administration. Life Sciences 72: 1665-1682, 2003.


Carmen Hinojosa-Laborde  
Associate Research Professor of Anesthesiology  
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The mechanisms of post-menopausal hypertension are not well understood and few animal models exist to study this phenomenon. In my laboratory, we use the Dahl Salt Sensitive rat as an animal model of post-menopausal hypertension to investigate the mechanisms responsible for the hypertension. The Dahl Salt Sensitive rat shares the common trait of salt-sensitivity with many post-menopausal hypertensive women. While many observations implicate a role for estrogen, the effects of aging on the regulation of blood pressure can also contribute to the development of salt-sensitive hypertension in postmenopausal women.

My research focuses on understanding how estrogen loss, aging and salt diet can result in the activation of pressor systems important in the development of hypertension. Two major controllers of blood pressure are the sympathetic nervous system and the renin angiotensin system. My studies are designed to determine how estrogen loss, aging and salt diet can alter the ability of the sympathetic nervous system and the renin angiotensin system to control blood pressure.

In our experiments, we record blood pressure and heart rate by radiotelemetry to determine the long-term effects of aging and estrogen loss in female rats when they are fed a low salt diet and a high salt diet. We assess the contribution of the sympathetic nervous system by recording sympathetic nerve activity, measuring circulating catecholamines, and by various pharmacological techniques. The contribution of the renin-angiotensin system assessed by measuring circulating levels of various components of the renin angiotensin system, and by pharmacologically blocking angiotensin receptors in the blood vessels. Molecular mechanisms of the regulation of the renin-angiotensin system are also determined.

Selected Publications


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Dr. Koek’s laboratory uses animal models aimed at aiding the development of medications for substance abuse. The models involve behavioral effects that range from directly observable (e.g., drug-induced motor impairment) to effects examined by operant conditioning procedures (e.g., discriminative stimulus effects, which are related to subjective drug effects in humans). The models are used mainly to examine the effects of alcohol and the club drug gamma-hydroxybutyrate (GHB), because alcohol abuse is a major public health problem, and because recreational use of GHB is increasing dramatically. One of the difficulties with treating alcohol abuse is that alcoholism is not a homogeneous disease entity. The laboratory focuses on early onset alcoholism, the subtype posing the most severe problems. Early onset alcoholism is often associated with poor inhibitory control, evidenced by increased impulsivity and aggression, that is exacerbated further by an increased sensitivity to the activating, disinhibiting effects of alcohol and by a decreased sensitivity to its motor impairing effects. These features, which result from interactions of genetic and environmental factors, involve decreased serotonin levels, increased neurosteroid levels, and altered functioning of GABA-ergic systems. Increased understanding of these underlying mechanisms will contribute to better treatment efforts. The pharmacological mechanisms by which GHB produces its abuse-related effects are poorly understood. GHB abuse is likely related to its subjective effects, and subjective effects of drugs in humans can often be predicted from drug discrimination experiments in animals. The discriminative stimulus effects of GHB are likely to involve several different receptor mechanisms. Some of these mechanisms may be unique to GHB (i.e., those involving specific GHB receptors), whereas others may be in common with other compounds (i.e., those involving GABAA and GABAB receptors). The laboratory examines the involvement of these mechanisms in the discriminative stimulus effects of GHB under various conditions (e.g., training dose, alternative training condition). By identifying the role of specific receptors in abuse-related effects of GHB, future studies may be better able to develop specific, pharmacologically targeted therapies for GHB abuse.
Selected Publications


John G. Kuhn, Pharm.D., FCCP, BCOP
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The research in our laboratories is concentrated on deriving information related to the preclinical and clinical pharmacology of anticancer and preventive agents. To accomplish our research objectives, we establish suitable analytical (HPLC, CE, LC/MSn) or molecular (PCR, Western, Elisa) methods for the measurement of the compounds in biological fluids or tissue. We also explore the relationships between the pharmacokinetic parameters (clearance, AUC) of the agent and their biological targets (AKT1,2,3, TNF•, NFkB), activity and/or toxicity. These correlations permit the development of rational dosing and scheduling regimens for the optimization of the compound's therapeutic index. In addition, we use in vitro systems (cDNA probes, human liver microsomes) and in vivo models (transgenic or knockout mice) to study the influence of the cytochrome P450 system and export pumps on the metabolism, elimination and activity of the anticancer agent under investigation. We also genotype for specific enzymes (2C9, 2D6) involved in the elimination or activity of anticancer agents. The laboratories also serve as the Pharmacology Core for the North American Brain Tumor Consortium.
Selected Publications


**Y.W. Francis Lam**  
**Associate Professor of Pharmacology and Medicine**  
**Clinical Associate Professor & James O. Burke Endowed Centennial Fellow in Pharmacy at the Univ. of Texas at Austin**  
**Pharm.D., University of Minnesota**

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Variability in pharmacologic response to a drug can be partially related to interindividual differences in pharmacokinetics, which can be modulated by an individual’s metabolic capacity and concomitant therapy. Development and availability of different in vitro systems over the years have allowed for identification of major cytochrome P-450 isoenzymes and assessment of enzyme inhibition potentials. My primary research interest is on the pharmacodynamic and pharmacokinetic consequences of cytochrome P-450 isoenzymes-mediated drug metabolism. In vivo probes of different isoenzymes
are used to investigate the intrinsic and extrinsic variants affecting metabolic capacity, and to investigate the therapeutic utility of metabolic profiling. These probes also allow an opportunity to further address possible genetic and environmental determinants of drug responsiveness among different ethnic groups.

**Selected Publications**


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Many drugs have important behavioral actions. One such behavioral action is drug addiction. Drug addiction results from the interactions between an individual’s ongoing and past behavior and the pharmacological actions of a drug. The behavioral pharmacology of drug addiction aims at understanding these interactions. Thus, behavioral pharmacology aims to understand how drugs affect behavior, understand how behavior affects drug action, and understand the pharmacological mechanism of these actions. Developing these understandings is fundamental to understanding the behavioral biology of drug addiction and to developing new and more effective treatments of drug addiction.

Ongoing studies address this both from a treatment development perspective and from a basic science perspective. Frequently, however, research is conducted that combines these two perspectives. Two examples of how these perspectives are combined are ongoing studies on the effects of serotonin re-uptake inhibitors on ethanol self-administration in rats and ongoing studies on shaping abstinence in smokers.

Selected Publications


Senlin Li  
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My primary research interest is to develop autologous hematopoietic stem cell (HSC) gene therapy, particularly HSC-derived macrophage gene therapy for neurodegenerative diseases, atherosclerosis and other inherited blood disorders.

Macrophages are recruited from bone marrow to most tissues of the body, including the central nervous system, thus making them an attractive option to deliver therapeutic genes. In macrophage-mediated gene therapy, HSCs will be mobilized from bone marrow, isolated by apheresis, and transduced ex vivo to establish stable expression of therapeutic genes. The transduced HSCs are given back to the same patients and thereafter graft will form various lineages of blood cells, including macrophages. Because they are under the control of macrophage-specific promoters, the therapeutic genes will be expressed at high levels of macrophages only. Neurotrophic factors can be beneficial to degenerative neurons, such as glial cell-derived neurotrophic factor (GDNF) to Parkinson's disease (PD) and nerve growth factor (NGF) to Alzheimer's disease (AD). Over-expression of apoE, apoAI, LXR (liver X receptor), etc. in macrophages has been shown to ameliorate atherosclerosis. These projects capitalize on the super-macrophage promoters that we have recently developed and lentiviral vectors that are superior in transduction of HSCs while maintaining their stem cell nature.

Recent advance in stem cell research has demonstrated the feasibility to produce patient-specific ES cells by nuclear transfer (ntES). Mouse ES cells have been differentiated in vitro into HSCs that can rescue lethally-irradiated syngeneic recipients. HSCs created by nuclear transfer can give old animals youthful blood cells. Taken together, ntES cells can be coaxed in vitro to HSCs that will rejuvenate the blood. Those HSCs will be the best carrier of the gene therapy described above.

Other ongoing projects in Dr. Li's laboratory include transcriptional regulation of PD-related genes, genome-wide mapping of histone acetylation in cancer cells, age-related oxidative DNA damage and repair, and cellular mechanism of parkin in neurodegenerative diseases.

Selected Publications


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Our primary interest lies in studying the insulin signal transduction pathway, which is activated when the hormone insulin binds to its cell surface receptors, resulting in a cascade of biochemical reactions that culminates in regulation of metabolic processes such as glucose uptake and glycogen synthesis. Defects in any of the steps along this signaling cascade can result in insulin resistance, one of the primary contributors to developing Type 2 diabetes. In order to better understand the molecular mechanism of insulin signal transduction and insulin resistance, we are using molecular biology, biochemistry, and cell biology approaches as well as animal models to identify and characterize signaling components involved in insulin receptor signaling processes. It is our hope that better understanding of the signaling components involved in mediating insulin signal transduction will generate information that may be contributed to the development of new therapeutic drugs for the treatment of Type 2 diabetes.

We are also interested in investigating the link between insulin signaling and aging. Recent studies from invertebrates suggested that reducing insulin/IGF-1 signaling in the neurons can extend the life-span of these organisms. Whether reducing neuronal insulin/IGF-1 signaling in mammals extends their life-span remains to be established. We are currently developing animal models in order to determine whether neuronal insulin signaling plays a role in regulating mammalian longevity and aging.

Selected Publications

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Liu, F. (2003) Grb10 Inhibits Insulin-stimulated Phosphorylation of IRS-1/IRS-2 and
Delays Akt Activation by Disrupting the Association of IRS-1/IRS-2 with the Insulin

and Ser399 is important for the activity and function of 3-Phosphoinositide-dependent

mediated p62dok tyrosine phosphorylation at Residues 362 and 398 plays distinct roles
for binding GAP and Nck and is essential for inhibiting insulin-stimulated activation of

Phosphorylation of PKN by PDK1 mediates insulin signals to the actin cytoskeleton.
My lab studies the neural circuits that regulate feeding and stress responses, as well as the neurochemicals expressed within these circuits. Our research emphasizes the interface between stress, emotionality and feeding behavior, and is presently focused on the functional organization of the central melanocortin system. One of unique characteristics of this system is the existence of a naturally occurring antagonist Agouti-related protein (AGRP), which binds to melanocortin 3 and 4 receptors to inhibit their responses to the endogenous agonist α-melanocyte-stimulating hormone (α-MSH). We are currently characterizing the upstream regulators and downstream targets of central melanocortin signaling, and determining how AGRP, α-MSH and their common receptors interact and coordinate feeding and stress functions. These issues are investigated using a combination of anatomical, pharmacological, behavioral and molecular tools. In addition, in collaboration with Dr. Wei Zhang, we have begun to utilize a viral vector-mediated gene transfer approach to manipulate expression levels of different melanocortin system components and related molecules in selected brain regions at specific development stages. These studies will have clinical implications at the interface between obesity, eating disorders and mood disorders. Given the genetic predisposition to these disorders, our studies of short- and long-term viral vector-mediated gene transfer will contribute to the development of potential therapeutic interventions to treat these illnesses.

**Selected Publications**


Lance McMahon
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Drug dependence can have devastating consequences not only for the dependent individual, but also for family, friends, public health, and society. Developing effective therapies for drug dependence requires an understanding of the environmental, behavioral, and pharmacologic determinants responsible for drug use. Research in my laboratory integrates principles of behavior and receptor theory to identify mechanisms in the nervous system responsible for the abuse liability of sedative-hypnotics, opioids, and cannabinoids.

Cannabis use, in particular, has received considerable scrutiny. From the perspective of public health, cannabis appears to have some therapeutic value on the one hand and deleterious effects on performance and quality of life on the other. Current research emphasizes:

1) Mechanism(s) of cannabinoid action. The effects of cannabis that lead to its self-administration are hypothesized to be mediated by a common mechanism at a particular cannabinoid receptor subtype. Results of ongoing studies suggest that a single mechanism does not account for the behavioral effects of cannabinoids.

2) Dependence that results from chronic cannabinoid treatment. Learned behavior is being used to better understand the neuropharmacology of cannabis dependence, as
defined by withdrawal upon discontinuation of cannabinoid treatment, and to identify medicines that might alleviate withdrawal in those seeking to achieve abstinence in the clinic.

**Selected Recent Publications**


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**Steven W. Mifflin**  
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My laboratory is investigating how the central nervous system regulates blood pressure and respiration in normal and pathological states. Arterial baroreceptors and chemoreceptors provide the brain with a constant barrage of information regarding the
level of blood pressure and blood gases, respectively. The brain processes this information to maintain blood pressure and blood gases within "normal" levels. We are using a multi-disciplinary approach to determine how baroreceptor and chemoreceptor information is integrated within the nucleus of the solitary tract (NTS), the initial site in the central nervous system to receive baroreceptor and chemoreceptor information. In vivo (intracellular and extracellular) and in vitro (whole cell patch clamp) electrophysiological techniques are used to examine the physiological and pharmacological mechanisms which underlie the integration of baroreceptor and chemoreceptor inputs by neurons of the NTS. Immunohistochemical techniques are used to determine the relationships between functionally identified neurons and putative transmitters or modulators. Molecular biological techniques are used to examine alterations in the expression of ligand-gated and voltage dependent ion channels in hypertensive and hypoxic rats and to phenotype neurons studied in vitro. These studies will advance our understanding of blood pressure and respiratory regulation under normal conditions and provide insights into the etiology of pathophysiological states where the brain does not regulate blood pressure normally (e.g. hypertension, heart failure).

Selected Publications


Stephen B. Milam  
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Ph.D., UTHSCSA  

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My current research is focused on specific cell-extracellular matrix interactions that may influence neuronal signaling. At the present time, we are exploring the potential role of integrins, transmembrane receptors that bind specific extracellular matrix molecules, as regulators of mechanoreception in trigeminal nociceptors. These studies involve both in vitro and in vivo models of mechanical nociception, and employ a variety of biochemical, immunological, pharmacological, and genetic methods. Our laboratory is one of three facilities in the world equipped to perform magnetic twisting cytometry studies at the single cell level. This method permits us to apply known forces to cells via targeted receptors (e.g., integrins). The method also allows for the determination of physical cell membrane properties in response to mechanical or chemical stimulation.  

We are also examining integrin-dependent mechanisms that may regulate the establishment of functional cellular microdomains involved in opioid receptor signaling in cultured trigeminal nociceptors. Methods employed in these studies include RIA, EIA, real time PCR, IHC, ISH, Western blot, supramolecular complex isolation, and confocal microscopy.

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The focus of research in our laboratory is on the regulatory interactions between brain neurotransmitter systems, particularly those involving the central noradrenergic system.  

Central norepinephrine (NE) is an important neuromodulatory transmitter, which plays a critical role in the response to stress by influencing arousal and sensorimotor response characteristics, and by integrating autonomic and endocrine responses with behavior.  

One of our main projects, using the techniques of in vivo microdialysis and behavioral pharmacology, is an investigation of the role of NE in modulating anxiety-like behavioral and neuroendocrine responses to acute stress. At a molecular and cellular level, we also study regulatory changes in gene expression that occur in brain noradrenergic neurons in response to stress, including expression of mRNA for synthetic enzymes, the NE transporter and post-synaptic adrenergic receptors using in situ hybridization. A related area of interest is the interaction between genetic predisposition to stress
susceptibility and the occurrence of sensitizing environmental stimuli to produce changes in the brain noradrenergic system that may contribute to the development of stress-related diseases such as depression, PTSD or anxiety. Brain NE is co-localized with a number of neuropeptide transmitters such as NPY and galanin, and we also examine the regulation of expression and function of these peptides in the context of acute and chronic stress. Another major effort is to understand the regulatory changes in neurotransmitter function that underly the therapeutic effects of antidepressant and anxiolytic drugs. These studies will help us to better understand the differential roles of NE and co-localized transmitters in complex physiological contexts such as the stress response, and the long-term regulatory interactions that occur between transmitter systems. This work is also aimed at better understanding the influence of these neurotransmitters in stress-related pathology such as anxiety or depression, and in the mechanism of action of psychotherapeutic agents such as antidepressants.

**Selected Publications**


Ravi Ranjan
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The genetics of aging in Drosophila and the mechanism of neurotransmitter secretion at the synapse

Overview: The roots of cognition, behavior, learning and memory are embedded in the brain’s intricate network of neuronal cells and their specialized points of contact, the synapses. Alterations in synaptic signaling underlie a variety of forms of synaptic plasticity associated with learning, memory, and aging and have important roles in the pathogenesis of age-related neurodegenerative disorders, including Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, epilepsy and stroke. My research interests can be divided into two parts a.) What are the molecular mechanisms underlying coordinated behavior, cognition, learning and memory? b.) How are these mechanisms affected by inherited neurological diseases and age-related neurological decline? The focus of my research is to comprehensively elucidate the molecular mechanisms underlying synaptic function, plasticity, and aging. We are combining molecular biology, electrophysiology, imaging and behavioral approaches with Drosophila genetics to investigate the molecular mechanisms involved in neuronal signaling and the underlying changes that cause neurological diseases and neuronal aging.

There are two primary areas of research within my laboratory:

A.) Genetic dissection of synaptic plasticity and aging: We are focusing on a provocative G-protein coupled receptor (GPCR), Methuselah, previously shown to increase lifespan.

B.) Genetic dissection of Ca\(^{2+}\)-regulated neurotransmitter release: We are studying the family of proteins containing C2 domains, particularly synaptotagmin, and their roles in membrane traffic.

A.) G-Protein dependent synaptic modulation: In biological systems, physiological responses to extracellular signals are elicited by activation of specific receptor proteins such as G-protein coupled receptors (GPCRs). Important modulatory roles for GPCRs have been suggested for aging, sleep, synaptic release and other cellular responses. Adaptive modifications of synaptic efficacy are very important for normal brain functioning and this is accomplished by signaling cascades. G-protein coupled receptors are important members of these processes.

Methuselah: Methuselah mutants were isolated in a screen for mutations affecting resistance to stress and aging. Methuselah loss-of-function mutations increase lifespan by 35% and also increase stress resistance. Our analysis of synaptic transmission at the fly larval neuromuscular junction revealed that methuselah mutants have reduced
transmitter release and indicate that Methuselah is a modulator of release, perhaps altering a step downstream from Ca\(^{2+}\) entry. We find an interesting paradox in this phenotype: all known synaptic mutants with a reduction in vesicle release die prematurely, unlike Methuselah, which lives longer. So far the relationship between aging and reduced release has not been addressed. This is an open and interesting problem currently being investigated in my laboratory.

Recently the ligands for Methuselah have been identified which encode for an \(\epsilon\)- subunit of ATP syntheses. Mutations in the ligands also extend lifespan and preliminary analysis suggests that they may modulate presynaptic release like methuselah. This early analysis provides convincing evidence that Methuselah, a G-protein coupled receptor and other components of its pathway may be very important for synaptic plasticity and subsequently for processes of neuronal aging. We are using \textit{Drosophila} as a neuronal aging model to understand the underlying mechanisms.

**Ongoing research**

Our current analysis revolves around four major questions concerning the role of Methuselah in synaptic release in relation to cellular plasticity. (1) Are the reduction in neurotransmitter release and aging causally related? (2) How do Methuselah and its ligands control synaptic release and aging? (3) How do these components interact with synaptic release machinery to modulate aging? (4) What are the downstream components of the Methuselah pathway regulating vesicle docking/priming? The systematic analysis of the Methuselah receptor, its ligands and newly found components of this pathway will enable us to understand how this pathway modulates the synapse. We are analyzing the known components and at the same time looking for new molecules by genetic interaction and screens.

**B.) Ca\(^{2+}\)-triggered vesicle fusion:** Since the discovery that Ca\(^{2+}\) is essential for fast, regulated neurotransmitter release, neurobiologists have been in search of the relevant molecules that sense the Ca\(^{2+}\) flux. In the past decade synaptic proteins such as SNAREs and Synaptotagmin I were shown to be central to the calcium triggered fusion. Yet despite considerable effort, the definitive roles of Synaptotagmin I and other key synaptic proteins have not been determined. The problem is made more complex by the fact that Synaptotagmins are members of a large family, most of which bind to Ca\(^{2+}\). Initial analysis suggests that family members may function in a combinatorial fashion to sense Ca\(^{2+}\) at a given synapse. We are exploring the role of individual synaptotagmin isoforms and the interrelationship between different isoforms to understand their synaptic functions. Beside synaptotagmins, we are in the process of analyzing novel synaptic genes and have begun genetic screens to identify additional components that function in synaptic transmission by directly screening for electrophysiological defects.

**Summary:** To comprehensively address the issue of synaptic vesicle exocytosis and its modulation, we have chosen \textit{Drosophila} as a model system which can be easily manipulated at multiple levels. I plan to combine genetics with molecular biology, electrophysiology, imaging and behavior. Systematic genetic dissection of these different genes will help in understanding their individual and combinatorial roles in synaptic plasticity and aging.
Selected Publications


James Roberts
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A major new area of research in the Roberts’ lab focuses on the role of estrogens, growth factors and cytokines in mediating protection of the brain from damage due to oxidative stress, focusing on the nigro-striatal pathway and its degeneration in Parkinson’s disease. Particular attention is given to the molecular and cellular mechanisms of action and signal transduction pathways activated. The positive and negative role of immune cell invasion into the damaged nigro-striatal area is also being investigated. This whole system is characterized from a perspective of the changes that occur as the animal’s age progresses.

Another major area of investigation deals with neuropeptide metabolism by the extracellular peptidases EP24.15 and 24.16. Our lab is investigating how these peptidases are trafficked intracellularly and how the enzymatic activity is regulated
utilizing model cell culture systems as well as the rodent trigeminal ganglion (TGG), a sensory neuronal tissue dealing with orofacial pain. The actions of the enzymes on GnRH, bradykinin and opiate peptides are being investigated. In a parallel set of studies, the role of estrogen in modulating orofacial pain in the TGG is being evaluated. Experiments are focusing on the recently identified plasma membrane estrogen receptor and its role in mediating estrogen’s enhancing effects in orofacial pain.

My research group comprises Dr. Benxu Cheng, Assistant Professor; Dr. Flávia Carreño, Postdoctoral Fellow; Yolanda Acosta, Research Associate; Alex Martinez, Research Assistant; Heather Daniels, Laboratory Technical Assistant II; and Mona Bains & David Price, Graduate Students.

**Selected Publications**

Khaing Z, **Roberts JL**, Blum M. Embryonic mesencephalon derived neurospheres contain progenitors as well as differentiated neurons and glia. Molec Cell Neuro, in revision.


The electrical activity of neurons and other excitable cells is generated by the combined action of chemically and electrically gated transmembrane ion channels. Most psychoactive drugs exert their effect by directly or indirectly modifying neuronal ion channel function in the brain. My research is aimed broadly at understanding the mechanisms by which ion channels are dynamically regulated and at elucidating the roles of pathological channel activity in neurological disease. The overall goal is to identify pathological states of ion channel function that may be targeted by pharmacological agents without interfering with physiological channel function.

My research specifically has focused on understanding the modulation of ion channels gated by the neurotransmitters glutamate and gamma-aminobutyric acid (GABA) and their roles in the generation of acute seizures and chronic epilepsy in the developing brain. Glutamate receptors mediate most fast excitatory synaptic transmission in the brain, whereas GABA receptors mediate most inhibitory transmission. Alterations in the function of either of these neurotransmitter systems can render the brain abnormally susceptible to seizures.

Using a combination of electrophysiological and molecular approaches, we are investigating how glutamate and GABA receptors are regulated during early development in the rat hippocampus. The immature brain is especially susceptible to seizures, and we have observed maturational differences in the molecular composition and function of glutamate receptors that are likely to contribute to this increased seizure susceptibility. Additionally, early life seizures increase the risk of chronic epilepsy, and we further have observed pathological changes in glutamate and GABA receptor function following generalized seizures in the neonatal rat.

Additional work is aimed at establishing a causal link between altered channel function and neuronal hyperexcitability using tissue culture preparations in which channel expression and function can be directly manipulated in the absence of previous seizures. A thorough understanding of the maturational and activity-dependent regulation of ion channels is necessary to develop optimal age-specific therapies to treat neonatal seizures and to prevent long-term epileptogenesis.

Selected Publications


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The Division of Clinical Pharmacology is based in the Departments of Pharmacology and Medicine and occupies offices and patient and analytical areas in the McDermott Building. The clinical commitment includes the Hypertension Service of the University Medical System. Clinical studies are based on this patient population.

Selected Publications  


Thomas Slaga
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The research in Dr. Thomas Slaga's laboratory is focused on glucocorticoid hormones (GC), very potent inhibitors of physiological DNA synthesis in keratinocytes in vivo. These hormones are also very effective in preventing carcinogen- and tumor promoter-induced skin hyperplasia, inflammation, and mouse skin tumor formation when applied to skin together with a carcinogen or a tumor promoter. We and others have shown, however, that the GC do not affect the growth of either established papillomas, squamous cell carcinomas (SCC), or transformed keratinocytes in vitro. In addition, we recently found that the GC do not affect glucocorticoid-responsive genes in transformed keratinocytes both in vitro and in vivo. We have generated skin-targeted transgenic mice over-expressing the GR under the control of the keratin 5 (K5) promoter. These adult transgenic mice have impaired proliferative and inflammatory responses to skin tumor promoters. Our initial studies showed that the K5.GR transgenic animals are resistant to ras-induced tumorigenesis. The constitutively nuclear overexpression and activation of the GR in the epidermis dramatically inhibited skin tumor development in K5.GR/ras+ double transgenic mice in terms of number of animals that develop tumors, number of tumors per animal, and tumor size. In another study we plan to determine the mechanism(s) of synergistic action of the natural source compounds, known to inhibit one or more stages of skin carcinogenesis, i.e., initiation and promotion/progression. The concurrent topical and systemic (i.e., dietary) treatment with selected natural source inhibitors of different stages of skin carcinogenesis result in synergistic effects.
leading to more efficient prevention of skin cancer. The natural source inhibitors to be tested include ellagic acid, imperatorin from the family of coumarins, proanthocyanidin B-2-gallate, (-)-epigallocatechin from the family of green tea polyphenols, N-acetylcysteine, calcium D-glucarate, lycopene, camosol and ursolic acid from rosemary extract, and resveratrol. We propose to initially utilize a number of very predictive short-term in vitro and in vivo tests in order to identify the mechanism(s) and to differentiate the potencies of selected inhibitors at various concentrations under standard conditions. The most effective compounds will then be studied in long-term tumor experiments utilizing a 7,12-dimethylbenz[a]anthracene (DMBA)-induced 12-O-tetradecanoylphorbol-13-acetate (TPA)-promoted multistage carcinogenesis model in SENCAR mice.

Selected Publications


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My research has two major objectives: the first is directed toward understanding receptor mechanisms involved in regulating tyrosine hydroxylase (TH) gene expression, the rate limiting enzyme in the synthesis of catecholamines. The latter substances are crucially involved in various life-sustaining functions and are implicated in diseases such as hypertension, depression and Parkinson's disease. We are examining the signal transduction mechanisms that mediate the effects of selected neurotransmitter and neuromodulators on TH gene expression in a cultured adrenal chromaffin cell line. Most recently, we have focused on vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide (PACAP) receptors and glucocorticoid receptors. We have investigated both transcriptional and post-transcriptional responses to PACAP and VIP and found that the PAC1 receptor distinguishes between the two agonists by stabilizing TH mRNA in response to PACAP, but not VIP. We are investigating intracellular signaling pathways in this response. We also recently identified the glucocorticoid responsive element in the promoter region of the TH gene. We are examining how second messenger...
pathways that are stimulated by neuropeptide receptors modulate the transcriptional responses to glucocorticoids.

The second research objective is directed toward understanding the role of oxidative stress in the aging brain. One project is aimed at determining how reactive catecholamine metabolites contribute to neuropathology of aging and Parkinson’s disease. We are particularly interested in the role that 3,4-dihydroxyphenylacetaldehyde (DOPAL) plays in degeneration of dopamine neurons. This highly reactive metabolite of dopamine becomes elevated in Parkinson’s disease and is neurotoxic. Rotenone, a pesticide that reproduces the pathology of Parkinson’s disease in rats, has been shown to elevate DOPAL in cultured cells. DOPAL is believed to be cleared by the mitochondrial aldehyde dehydrogenase (ALDH2). We have developed an ALDH2 knockout mouse to determine the role of this enzyme in DOPAL catabolism. We are also using this new mouse model to study the role of DOPAL in the pathology of Parkinson’s disease.

Selected Publications


LuZhe Sun
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Our laboratory studies molecular mechanisms that regulate carcinogenesis and cancer cell growth, invasion, and metastasis using molecular and cellular biology techniques and animal model systems. One of the molecules we are currently studying is called transforming growth factor beta (TGF beta). This growth factor has been shown to inhibit tumorigenesis and growth of some early-stage adenocarcinoma cells, yet promote growth and metastasis in late-stage carcinoma cells. We are trying to understand why a given polypeptide growth factor has such different effects and devising the means that can enhance its tumor-suppressing activity while antagonizing its tumor-promoting activity. We are particularly interested in developing a soluble form of TGF beta receptor as a TGF beta antagonist to suppress TGF beta-promoted tumor progression. Other projects in the laboratory include the investigation of how hormone signaling stimulates carcinogenesis in breast and prostate. Our approaches to study regulation of gene expression include transcriptional and posttranscriptional analyses with techniques such as gene microarray, promoter activity measurements, polymerase chain reaction, quantitative PCR, receptor cross-linking, immunoprecipitation and Western blotting analyses. To study gene functions, we use sense transfection, RNA interference, and retroviral transduction techniques to regulate gene expression and study the effects of altered gene expression on malignant phenotypes of cancer cells in tissue culture and in mice.

Professional Society Memberships

American Association for Cancer Research
American Society for Biochemistry and Molecular Biology
American Association for the Advancement of Science

Selected Publications


**Maharaj K. Ticku**  
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Dr. Ticku's major research goals are to understand and define the molecular mechanisms by which drugs modulate inhibitory and excitatory neurotransmitter systems in the mammalian central nervous system. GABAA and NMDA receptors belong to a ligand-gated super gene family. A major focus of our research is to determine the effect of chronic administration of benzodiazepines, barbiturates, neurosteroids or alcohol on regulation of GABAA receptor binding, function, gene and polypeptide expression. Chronic drug treatment could affect neurotransmission by down- or upregulation of receptors, altered coupling between various sites associated with oligomeric receptor complex and/or altered receptor efficacy. How alcohol regulates NMDA gene expression is a major focus.

These experiments are being conducted in mammalian cortical neurons under precisely controlled conditions and independent of pharmacokinetic variability. A second focus is the investigation of the effects of alcohol on NMDA receptor function and gene expression. NMDA receptors are involved in a variety of physiological processes, including maintenance of excitability, neuronal development, learning and memory as well as in the pharmacological effects of alcohol. A number of different experimental approaches are employed in these studies including receptor binding, 36Cl-flux, changes in intracellular Ca+2 levels, mRNA and polypeptide level measurements. Current research involves regulation of promoter activity of NMDA R2B gene by enhancers and silencing factors (Mol Pharm papers, 2005).

More recent studies include developing new probes (agonists, antagonists) to study how the date rape drug (GHB) works in the brain. These drugs have potential to be used for GHB intoxication.
Research Associates

Currently, Drs. A.K. Mehta (Research Assistant Professor), S.R. Kadapakkam (Research Scientist), S.K. Rani and Mei Qiang (Research Instructors), C.R.M. Ravindran (Postdoctoral Fellow), and Mr. Jason Hernandez are working in Dr. Ticku’s laboratory.

Societal Affiliations

Dr. Ticku is a member of many societies including ASPET; Society of Neuroscience; American college of Neuropsychopharmacology (ACNP); Research Society on Alcoholism; Collegium Internationale Neuro-Psychopharmacologicum (CINP); Society of Neurochemistry and ISBRA. He has chaired many national and international symposiums. Dr. Ticku’s research has continuously been funded by NIH/NIAAA since 1979. Additionally, Dr. Ticku has served on NIH-NINDS and NIH-NIAAA study sections, and Chaired many Special Review Committees of NIAAA. He also served as a consultant to United Nations. Dr. Ticku is currently the recipient of a MERIT Award from NIH-NIAAA (2000-2010).

Selected Publications


Maratha, RCV and Ticku, MK. Role of CpG islands in the up-regulation of NMDA receptor NR2B gene expression following chronic ethanol treatment of cultured cortical neurons of mice. Neurochem Int. 46: 313-327, 2005.


Kumari M, Ticku, MK. Regulation of NMDA receptors by ethanol. Prog Drug Res. 54:152-89, 2000.


Follesa, P. and Ticku, MK. Chronic ethanol-mediated upregulation of the NMDA receptor polypeptide levels in mouse cortical neurons in culture. J. Biol. Chem. 271:13297-13300, 1996.