

# **Department of Pharmacology**

Departmental Handbook for Trainees

2011-2012

UNIVERSITY OF ILLINOIS at CHICAGO  
COLLEGE OF MEDICINE

This handbook provides information about  
the Department of Pharmacology for  
graduate students.

Asrar B. Malik, Department Head  
Randal A. Skidgel and Thomas M. Guenther, Co-directors of Graduate Studies  
Cynthia Sanders, Director of Program Development



We welcome you to the Department of Pharmacology at the University of Illinois College of Medicine at Chicago. Research in our department focuses on several fields of study, including cardiovascular and lung biology, cell signaling, molecular pharmacology of G proteins, molecular and cellular basis of inflammation, and neuropharmacology. The department is also expanding its areas of study to include translational research and stem cell therapy. Faculty in the Department of Pharmacology receive extensive NIH funding, including the Lung Biology and Pathobiology Training Program. Students in our program receive didactic and research training that prepares them for future careers in science in academia, private industry or government. First year students participate in the Graduate Education in Medical Sciences (GEMS) program, which is an integrated approach to graduate education, comprising common core coursework and the flexibility to choose lab rotations in more than one department. In addition to didactic coursework and training in a wide variety of research techniques, students attend seminars given by preeminent visiting scientists, present their research to faculty and students and engage in numerous activities that provide the training necessary to become successful independent investigators.

Department of Pharmacology  
University of Illinois College of Medicine  
835 S. Wolcott Ave., Rm. E403 (MC 868)  
Chicago, IL 60612  
(312) 996-7635

Table of contents

<b>GENERAL INFORMATION .....</b>	<b>6</b>
New Students .....	6
Registration Procedures .....	6
Tuition and the Service Fee .....	6
Medical Immunization Records .....	6
The Chicago Transit Authority (CTA) U-pass program .....	2
Shuttle Bus Service .....	2
Parking .....	2
Graduate College Listserv .....	2
<b>FACILITIES .....</b>	<b>2</b>
Research Resources Center (RRC) .....	2
Biological Resource Laboratory (BRL) .....	3
Library of the Health Sciences .....	3
Academic Computing and Communications Center (ACCC) .....	4
Sport and Fitness Center .....	4
<b>SERVICES .....</b>	<b>4</b>
Family Medicine Center .....	4
Graduate Assistant Dental Program .....	5
Counseling Center .....	5
<b>SAFETY AND SECURITY .....</b>	<b>5</b>
<b>Laboratory Safety .....</b>	<b>6</b>
Radiation Safety .....	6
Emergency Procedures .....	6
After-Hours Access to Buildings .....	6
<b>DEPARTMENTAL RESEARCH FACILITIES AND SERVICES .....</b>	<b>6</b>
Study Areas and Lunchroom .....	7
Photocopy Service .....	7
Keys .....	7
<b>DEPARTMENT OF PHARMACOLOGY FACULTY &amp; STAFF .....</b>	<b>8</b>
Emeritus Faculty .....	10
<b>Graduate Studies Coordinator .....</b>	<b>10</b>
Function of Departmental Office, Room E403 MSB .....	10
Departmental Committees .....	12
<b>FACULTY RESEARCH INTERESTS .....</b>	<b>12</b>
<b>GRADUATE STUDIES .....</b>	<b>24</b>
Overview .....	24
Formal Course Work Requirements .....	24
<b>FIRST YEAR PHARMACOLOGY COURSES .....</b>	<b>24</b>
<b>SECOND YEAR PHARMACOLOGY COURSES .....</b>	<b>25</b>
Pharmacology Electives .....	25
<b>THIRD AND SUBSEQUENT YEARS .....</b>	<b>26</b>
<b>REQUIREMENTS FOR MD/PHD STUDENTS .....</b>	<b>26</b>
<b>GENERAL INFORMATION AND POLICIES .....</b>	<b>26</b>
<b>Academic Standards and Probation .....</b>	<b>27</b>
Advisors .....	27
Lab rotations: Affiliation with thesis advisor .....	27
Research Forums .....	28
Establishment of Departmental Research Committee .....	28
Graduate College Preliminary Examination .....	28
Thesis Committee and Defense .....	28

Expectation of Publication .....	30
Academic Integrity .....	30
Plagiarism .....	30
Attendance at Departmental Seminars and Special Lectures .....	31
Vacation .....	31
Postgraduate Placement Ads .....	31
Disposition of Laboratory Notebooks.....	32
<b>TRAINING GRANTS.....</b>	<b>32</b>
Student Awards.....	32
Graduate Student Travel .....	34
<b>CURRENT GRADUATE TRAINING PROGRAM .....</b>	<b>35</b>

## GENERAL INFORMATION

### New Students

New students should report to Cynthia Sanders in Room E403 MSB and provide a local address and telephone number. All students are assigned a mail box in the department office and are encouraged to maintain close contact with the departmental office for messages and notices. In addition, students should check the bulletin boards for announcements of seminars and important news items. This should be done several times a week since seminars are sometimes arranged on short notice. The bulletin boards are located in the main corridor next to Room E403.

After registering for classes in the first term, the student will obtain an i-card (UIC identification card) in Room 241 Student Center West (828 S. Wolcott) between 8:30 AM and 4:00 PM Monday through Friday; telephone number is (312) 413-5944. For building access see Charla Henry.

Salary and stipend checks are available on the 16th of each month. Students must arrange for direct deposit through NESSIE (the UIC Human Resources online system). The GEMS Program Administrator will instruct new students in using NESSIE to set up their payroll record. Kathy Andrykowski will instruct students going directly into Department of Pharmacology laboratories. The payroll stub can be printed from NESSIE.

### Registration Procedures

To register, visit my.UIC at <https://my.uic.edu/common/> New students will be advised for which courses to register by Dr. Tom Guenther, Director of Graduate Studies. After the first year, all students will register for PCOL 595 - Research Seminar and PCOL 599 – PhD Thesis Research in fall and spring semesters. In summer, most students will register for PCOL 599 to maintain eligibility for their assistantships. A total of 12 credits (6 in summer) are required to maintain eligibility for assistantships and/or tuition waivers. Some fellowships may require registration of 12 hours (6 in summer). (See course load information: <http://grad.uic.edu/cms/?pid=1000035> on the Graduate College web site.) Students are responsible for their own registration process and for meeting deadlines published in the Timetable.

**Tuition and the Service Fee** and Academic Facilities Maintenance Fund Assessment are covered by a waiver with assistantships and fellowships each term. As of Fall 2011, the departments will pay the students' other fees each term. In Fall 2011, the fees are as follows: general fee (\$426), health service fee (\$90) and health insurance fee (\$401), U-Pass fee (\$109) and the student to student fee (\$3). Late registration fees are the responsibility of the student. The Office of International Service also charges certain fees to international students. The health insurance fee may be waived yearly at the beginning of fall semester by providing proof of other medical insurance coverage (see: <http://www.uic.edu/hsc/campuscare/>). Fall and Spring terms, \$125 of the health insurance fee is covered by the Provost.

**Medical Immunization Records** are required by Illinois state law. All students are required to present documented proof of immunity against the following diseases:

Measles (Rubeola) - two doses at least 30 days apart

Rubella (German Measles)

Mumps

TD (Tetanus and Diphtheria) - three doses, one of which must be within the past ten years.

Those students who are not properly immunized and have not submitted a written statement of medical or religious exemption are required to undergo immunization within the first term of enrollment. Failure to provide the required proof of immunity will prevent a student from enrolling in a subsequent term. Questions pertaining to the medical immunization requirements may be directed to the Office of Medical Immunization Records, (312) 413-0464.

**The Chicago Transit Authority (CTA) U-pass program** is mandatory. As of Fall 2011, the fee assessed by the university, currently \$109 per student per semester is paid by the department. The CTA U-Pass is issued to eligible graduate students who are registered for **9 hours in Fall and Spring semesters, 5 hours in Summer**. The CTA U-Pass will be active for unlimited travel on CTA trains and buses five days prior to the term, and five days after finals week. The i-card is required to pick up the CTA U-Pass at the U-Pass distribution station at the Student Services Building at 1200 W. Harrison in the i-card office one week before classes start.

For more information visit, <http://www.vcsa.uic.edu/MainSite/departments/Upass/home/>.

### **Shuttle Bus Service**

Shuttle bus service from a number of locations between the west and east sides of the campus is available without charge. (Look for the buses with red signs, "Intercampus Shuttle"). You must show an i-card to board the bus. Commuter bus service is also available between the campus and the Metra train stations downtown free of charge. (Look for the bus with white sign, "Train Station Only"). Routes and schedules are in the Staff Directory and on the UIC web site. Commuter shuttle service may change during the 2011-2012 academic year. Please watch for email notifications or check: <http://fmweb.fm.uic.edu/Trans/commuter.aspx> for updates.

### **Parking**

Visitor lots are available to faculty, staff, students, and visitors to campus at the applicable hourly rate. Space availability in the visitor lots is on a first-come, first-served basis. There is very little street parking available. If you are parked illegally, your car may be ticketed or towed. After three parking tickets, the City of Chicago will immobilize your car with a Denver boot and you will have to pay all fines and a fee to have it removed.

If you wish to park a car on campus, a yearly parking assignment will cost \$863 annually (\$335 per semester). This fee is payable by cash, check, or credit card (Visa, MasterCard or Discover) when you apply. For your convenience, you may apply for parking at the east side parking office or either of the west side parking offices at 828 S. Wolcott, room B5. Parking is sold on a first-come, first-served basis. If you visit the office mid-semester, parking will be sold based on availability and at a prorated rate. Please bring your university i-card and payment fee with you at the time of your parking purchase. If you will need parking in the spring, please keep your hangtag. For parking lot locations and rate information, visit: <http://www.uic.edu/depts/avcad/parking/>

### **Graduate College Listserv**

The Graduate College posts important announcements on the Graduate College Listserv ([gradlist@uic.edu](mailto:gradlist@uic.edu)). For directions please visit: <http://grad.uic.edu/cms/?pid=1000070>

### **FACILITIES**

#### **Research Resources Center (RRC)**

The RRC works with research and teaching departments to obtain, maintain, and support high technology and scientific research equipment. It provides training, instrumentation for user operation, services and expertise in the application of a wide range of instrumental techniques for chemical, biological, and structural characterization. The availability of computational and statistical methods for data handling and interpretation of experimental results, and the services of electronic and mechanical

shops enable researchers to design and perform sophisticated experimental protocols.

RRC administrative offices and most of the RRC west campus facilities are located in the Medical Sciences Building, 1<sup>st</sup> floor and basement at 835 S. Wolcott Ave. Facilities on the east campus are located in the Science and Engineering South Building at 845 W. Taylor St.

The following is a list of facilities and services provided by RRC: Confocal Microscopy, Electron Microscopy, Flow Cytometry and Sorting, Transmission EM, Scanning EM, Mass Spectrometry, Nuclear Magnetic Resonance, Scientific Computing, Electronics Shop, Mechanical Shop, Transgenic Mouse Facility, Tumor Bank, Acquisition of Animals, Housing, Surgical Suites, DNA Sequencing, Oligonucleotide Synthesis, Flow Cytometry and Sorting, Protein Sequencing, Peptide Synthesis, Peptide Mapping, and Biostatistics. Use of the facilities and payments of charges should be coordinated through your adviser.

### **Biological Resource Laboratory (BRL)**

The BRL at 1840 W. Taylor is the campus unit that oversees the procurement, care, and maintenance of animals used in teaching and research programs of the University. This oversight responsibility includes insuring that the UIC programs meet the federal regulations, the requirements of the American Association for the Assessment and Accreditation of Laboratory Animal Care, and currently accepted standards for providing adequate veterinary care and proper animal husbandry. The professional staff is also responsible for providing advice to the research and teaching staff, conducting graduate and technical courses, and supporting the protocol review system of the Animal Care Committee.

The centralized animal facility of the Biologic Resources Laboratory has 104,000 sq. ft. of animal housing and support space. In addition to the central facility, the BRL also includes a 3,600 sq. ft. barrier facility for housing rodents in the recently completed Molecular Biology Research Building. A new barrier facility has opened in the College of Medicine Research Building (COMRB), which will provide specific pathogen free mice.

The UIC Program is accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC) and has consistently received positive evaluations from representatives of the Food and Drug Administration, the World Health Organization, the National Institutes of Health and several commercial pharmaceutical and contract laboratories.

Courses on the use of animals in research offered by the Graduate College and taught by BRL staff are:

GC 470 - ESSENTIALS FOR ANIMAL RESEARCH. 1 credits. S/U grade only. This course will acquaint the students with the regulations, sources of information, humane principles, and ethical considerations involving the appropriate use of animals for research and teaching purposes. **This course is required of all graduate students whose research involves the use of animals.**

GC 471 - EXPERIMENTAL ANIMAL TECHNIQUES. 2 credits. Animals used in instruction. S/U grade only. Noninvasive and invasive techniques commonly used in laboratory animals are performed with emphasis placed upon the proper use of anesthetic, analgesics and aseptic techniques. Prerequisite: GC 470.

GC 473 - SEMINAR IN COMPARATIVE MEDICINE. 1 to 2 credits. S/U grade only. Selected fields of interest and research in comparative biology, model development and experimental techniques. Prerequisite: GC 471 or consent of the instructor.

### **Library of the Health Sciences**

The Library of Health Sciences (LHS), 1750 West Polk Street, one of the largest medical libraries in the United States, supports education, research, and clinical practice in the health sciences. LHS also serves as the regional medical library for ten Midwestern states. LHS-Chicago's collection is comprehensive in the health sciences.

Library materials may be located in either the online catalog (UICCAT) or ILLINET Online (IO), a statewide library system. UICCAT, which contains records for over one million titles, can be searched by author, title (including journal titles), call number, Library of Congress Subject Headings, National Library of Medicine Subject Headings, and keyword. IO, a catalog that contains the bibliographic records for approximately 800 libraries in Illinois, enables users to check the circulation status of holdings at over 40 participating libraries at UIC, including LHS. Faculty, staff and students can also use their Academic Data Network (ADN) computer accounts to access UICCAT or IO from their offices, computer labs, and homes. There are currently several thousand full text journals available online through the LHS Web site.

Library users have access to the library catalogs of Committee on Institutional Cooperation (CIC) universities (the Big Ten schools as well as the University of Chicago and UIC). Materials cataloged in UICCAT, IO, and the catalogs of the CIC universities may be borrowed by faculty, staff and students by making a request via electronic mail (LIBMAIL), at any circulation desk, or while searching IO. Or, use the qUICsearch utility to search multiple databases at once. The Reference dept. offers training in searching PubMed and other bibliographic instruction at workshops or one-on-one. To set up your own library portal to collect the resources you use most often in one place, go to the Library Services Web page, <http://www.uic.edu/depts/lib/services/>.

#### Interlibrary Loan Service

Any materials not held by CIC universities or IO institutions, including books, journal articles, government documents and multimedia, may be borrowed from another library through the Interlibrary Loan Service. The library absorbs the cost of this service for faculty, students, and staff.

#### **Academic Computing and Communications Center (ACCC)**

You are responsible for opening an ACCC account to use email, Web publishing, and other computer services. Email is a frequently used tool of communication between the department and students and should be checked regularly. ACCC will automatically provide new students' netids and list students in the online phone directory when you open an account. First, obtain an i-card and then follow the steps on the ACCC Accounts Web site, <http://www.uic.edu/depts/accc/home/ACCTS.html> panel. If the online account opening utility does not work for you, you must visit ACCC Consultants located in the Benjamin Goldberg Research Center (BGRC), 1940 West Taylor St. There are also public computer labs in BGRC, open 24 hours with authorized keycard access. Fill out a building access form in BGRC room LL55 and allow 1-2 weeks for processing. You can purchase site licensed or discounted software through ACCC for your computer.

**Sport and Fitness Center** is adjacent to Student Center West (SCW). Visit [http://www.uic.edu/depts/recreation/facilities\\_sfc.shtml](http://www.uic.edu/depts/recreation/facilities_sfc.shtml) for more information. Students also have access to the Student Recreation Facility at 737 S. Halsted.

#### **SERVICES**

##### **Family Medicine Center**

The student health fee in your tuition pays for many services at the Family Medicine Center located in the Outpatient Care Center at 1801 West Taylor Street, 4E and at 722 W. Maxwell St., phone: (312) 996-2901, <http://chicago.medicine.uic.edu/cms/One.aspx?portalId=506244&pageId=4013129>

The Family Medicine Center provides the following services to all students when medically necessary and appropriate: Preventive health care services; Gynecologic preventive care at approved intervals; Common sexually transmitted disease care (including HIV testing and counseling); Contraception with student formulary covered medications, pregnancy counseling, and urine testing; Vision screening and hearing testing as provided by Family Medicine; Physical exams and PPD skin testing as required by the student's college; Administration of student provided desensitization injections; Tetanus booster if indicated and available; Acute care services when rendered during Urgent Care periods (available 9:00 A.M.-4:30 P.M., Monday-Friday, and 9:00 A.M.-noon on Saturday). Care is arranged by appointment and you should bring your student i-card and current class schedule. Emergency medical care and certain other medical treatments are not covered by student health, but the Family Medicine Center is also a preferred provider under CampusCare, the private medical insurance plan offered to students. Questions may be addressed to CampusCare at 996-4915 for administrative issues and 996-2901 for medical issues.

<http://www.uic.edu/hsc/campuscare/> or at the FMC 355-4185.

### **Graduate Assistant Dental Program**

The Graduate Assistant Dental Program is available for eligible students. This program is offered through a partnership with the College of Dentistry. For more information and eligibility requirements visit,

<http://www.uic.edu/depts/hr/uicdr/reasons/gradBenefits.html>. The Faculty Dental practice office telephone number is (312) 355-1401.

### **Counseling Center**

Students experiencing uncertainties and difficulties of a personal, educational, or vocational nature may seek counseling at the University Counseling Center in room 2010, Student Services Building, 1200 W. Harrison, 996-3490. If you need help with a personal crisis and the University is closed, you can telephone the In-Touch Hotline, 996-5535, 6:00 p.m.- 10:00 p.m., seven days a week. The Hotline's staff of student volunteers is trained and supervised by the Counseling Center to offer assistance and referral information. Web site: <http://www.uic.edu/depts/counseling/>

### **SAFETY AND SECURITY**

Departmental laboratories and teaching areas contain expensive equipment as well as chemicals and drugs which may be dangerous to those who are not trained in their proper use. Controlled substances must be kept in the departmental safe. Inventories to account for the usage of these substances must be maintained. All university buildings are open only to individuals who conduct business in the building. Surveillance is carried out by campus police. Rooms should be locked when not in use; the building is locked by campus police after daytime working hours. Please keep your space locked when not occupied. Each student is supplied with the necessary i-card to verify his or her right to use the building for study and research at any time.

The "Red Car" is a safety escort service available to University faculty, staff, and students. The "Red Car" operates from 11:00 p.m. to 7:00 a.m. seven days a week within the following general boundaries: Halsted Street on the east, Western Avenue on the west, Eisenhower Expressway on the north, and Roosevelt Road on the south. Your i-card must be presented to the driver when boarding. For service, call 6-6800 on campus. A lead time of one hour is suggested for individuals requiring Paratransit Service. The web site is: [http://fmweb.fm.uic.edu/Trans/red\\_car.aspx](http://fmweb.fm.uic.edu/Trans/red_car.aspx)

We ask your assistance in helping to preserve building security to ensure a safe environment by doing the following after normal working hours:

- close open windows which might provide access to intruders

- close doors that are taped or propped open
- report any incidents of strangers in the building after normal working hours to Campus Security (Ext. 6-2830)

### **Laboratory Safety**

Students should be aware of laboratory safety protocols, such as proper attire, protective eyewear and clothing, location of eye wash stations and emergency phone numbers. More detailed information about laboratory safety can be found at <http://www.uic.edu/depts/envh/>. You may be required to log in with your net id. It is imperative that you wear safety goggles, gloves and a lab coat when dispensing organic solvents and corrosive chemicals. Laboratories using these chemicals are required to be equipped with suitable devices for emergency eye washes and spill clean-up kits.

### **Radiation Safety**

State and federal regulations require training of all personnel who work with radioactive materials. The license of UIC requires training consisting of six hours of lectures provided by the Radiation Safety Office, supplemented by specific work-related instruction provided by the Radiation Project Director or supervisor. These lectures also qualify for the Illinois Department of Nuclear Safety's continuing education credit for Radiography, Nuclear Medicine and Radiation Therapy technologists. All students who intend to work with radioactive materials are required to attend these lectures, after which a certificate of attendance is issued.

### **Emergency Procedures**

**Police: Dial 5-5555 Non-emergency: Dial 6-2830**

**Fire: Dial 6-FIRE (6-3473)**

**Medical: Dial 5-5555**

**Environmental Health and Safety Office: Dial 6-SAFE (6-7233)**

Familiarize yourself with the locations of fire extinguishers and other emergency resources, e.g., fire alarm boxes, eye wash stations, and showers. Fires should be reported immediately by dialing 6-3473 and notifying the departmental office. In case of serious fires or fires producing extensive smoke or toxic fumes, the fire alarm should also be sounded. Even if a small fire can be controlled with a fire extinguisher in the laboratory, the incident should be reported to the departmental office and an order placed to have the extinguisher recharged.

A medical emergency requiring an ambulance or a physician should be reported by dialing the police, 5-5555. Other medical emergencies should be dealt with at the Emergency Room of the hospital at 1740 West Taylor Street. All injuries, whether requiring emergency care or not, should be reported to the departmental office.

### **After-Hours Access to Buildings**

During the night and early morning hours, as well as on holidays, access to the university is restricted to computer activated key card. Your i-card can be coded for entry at appropriate doors by applying with the help of Charla Henry. Access is also available at the University Police Station located in the basement of 840 S. Wood Street. If your i-card does not work, call 355-3529. Access to the Biological Resources Laboratory (BRL) is granted only through BRL staff.

## **DEPARTMENTAL RESEARCH FACILITIES AND SERVICES**

The research laboratories of departmental faculty members are listed as indicated on the faculty

directory, page 8. Each laboratory has advanced and sophisticated equipment for conducting biomedical research in specific areas. In addition, there are a number of multi-user major pieces of equipment in core areas. The research interests of the faculty are discussed on pages 12-23.

All research laboratories are the administrative responsibility of the department. Responsibility for individual laboratories and their inclusive equipment is delegated to the faculty member currently residing in that space. Within the departmental space there are shared research facilities (e.g., cold rooms, ultracentrifuges, refrigerated centrifuges, liquid scintillation counters, etc.) that are available to all members of the department, providing they have adequate knowledge for operation of these instruments.

Because of the great expense of many of these instruments and the severe and expensive damage that can result from improper operation, students are asked not to use any instruments unless they have been approved as qualified operators.

### **Study Areas and Lunchroom**

The Departmental Seminar Room, 419 CMW, may be used by graduate students for study purposes when the room is not in use. The Library of the Health Sciences as well as the Student Center and Benjamin Goldberg Research Center (BGRC) have areas that may also be used for study. Students can also utilize the GEMS space on the 3<sup>rd</sup> floor of the Clinical Sciences North building for studying and eating. Computer terminals are available for student use.

### **Photocopy Service**

The departmental photocopy machine in room 407 CMW is intended for the research activities of members of the department. The copier is available for student use with permission of his/her advisor. Each advisor has an access number and is billed quarterly for photocopy expenses. Copy machines are available in the Health Sciences Library and in the Student Center West for those who need copies for other purposes.

### **Keys**

Request for keys are to be cleared through your advisor and the department head. The form can be obtained from and returned to the main office. All keys are part of the departmental inventory and **MUST BE RETURNED TO THE OFFICE**, not the advisor, before a student receives clearance at graduation time. Please see Amina Chavero to request keys.

DEPARTMENT OF PHARMACOLOGY FACULTY				
Faculty				
NAME	E-mail	RANK (PRIMARY APPT)	ROOM	EXT.
Bonini, Marcelo	Mbonini	Assistant Professor (Cardiology) Ofc. 3035	3020 COMRB	5-5948/ 6-4147
Carnegie, Graeme	Carnegie	Assistant Professor	5091 COMRB, 5080 Lab	5-4435/ Lab 5-5936
Cho, Jaehyung "Gus"	Thromres	Assistant Professor	5095 COMRB, 5080 Lab	5-5923/Lab 5-5935 (Intravital/E423 /5-2409)
Colamonici, Oscar	ocolamon	Associate Professor	410 CMW/418 CMW/ 404 CMW	3-4113 / lab 3-2494 /6-4318 / 3-4140 fax / 5-4376 fax / 5-0966
Du, Xiaoping	xdu	Professor	4131/4120 COMRB	5-0237 / 5-0250
Erdős, Ervin G.	egerdos	Professor	427 CSN	6-9146 / 6-9181 / 6-1648 fax
Fukai, Tohru	tfukai	Associate Professor (Cardiology)	4095 COMRB/4080	6-7631/lab 6-7622
Guenther, Thomas	tmg	Professor	E418 MSB	6-2558
Hu, Guochang	gchu	Assistant Professor	544 CMW/521-23 CMW	6-4692/lab 5-2719
Komarova, Yulia	ykomarov	Asst. Prof.	4053/4040 COMRB	6-1332/lab 5-5942
Kozasa, Tohru	tkozasa	Associate Professor	5100 COMRB	3-0111/ 5-4277
Le Breton, Guy C.	gcl	Professor	768 CME/ 769 CME	6-4929 / 6-4983/ 6-1296 fax
Lyubimov, Aleksander	lyubimov	Director, Res. Ass. Prof.	1306A CME	6-2123
Malik, Asrar B.	abmalik	Distinguished Professor and Head	E403 MSB	6-7635 (I/C 02)
Mehta, Dolly	dmehta	Associate Professor	E411/E412MSB E414/E416 404 CMW	5-0236/lab 5-0241 6-4318/Monica, Tracy
Minshall, Richard	rminsh	Associate Professor	E417/E420/ E410B MSB	6-1655/ 410 lab 3-7866/ 420 lab 3-5561/confocal 6-6057
Natarajan, Viswanathan	visnatar	Professor	Ofc. 3137/3139/3140 COMRB LAB	5-5896, (Lab 5-5891, 5-5893) Karen Gordon 6-5023
O'Bryan, John P.	obryanj	Assistant Professor	4091COMRB/ 4060	6-6221/ lab 6-6858 Xuerong (6-6827)
Park, Changwon	pcwkyh17	Assistant Professor	4135 COMRB/4140 COMRB	5-4439/ lab 5-2568
Rehman, Jalees	Jalees	Visiting Associate Professor (Cardiology)	4113 COMRB/4100 COMRB	6-5552/lab 6-5793
Radulovacki,	mradulo	Professor	415 CMW/ 411	6-3539 /3-8461

Miodrag			CMW	
Skidgel, Randal A.	rskidgel	Professor	406A CMW/ 406 CMW/420CMW 409B CMW	6-9179 /lab 6-2157/ 6-7875/ 6-0374
Tiruppathi, Chinnaswamy	tiruc	Associate Professor	E401/E408/E406 /E407 MSB	5-0249/ lab 3-9640, Bin 5-3610
Ushio-Fukai, Masuko	mfukai	Associate Professor	4097 COMRB/4080	6-7665/ lab 6-7622
Wary, Kishore K.	kkwary	Assistant Professor	4051 COMRB/ 4140	3-9582, (Lab 6-9809)
Xu, Jingsong	jingsong	Assistant Professor (Dermatology)	4160 COMRB/ 4099 COMRB	6-6919/ Lab 5-3194
Yuan, Jason	Jxyuan	Professor	Ofc. 3113, 3131, 3120 Lab COMRB	5-5911/lab 5-5912 Fax: 6-7193
Ye, Richard	yer	Professor	4141/4143/4160 COMRB	6-5087 /lab 6-5678/ Pam 3-0239/6-7643/Fax6-7857
Zhao, You-Yang	yyzhao	Assistant Professor	4035 COMRB/4100 COMRB	5-0238/lab 6-1343

## **Emeritus Faculty**

Anderson, Edmund G.

Erdős, Ervin

Marczynski, Thaddeus J.

Isaac, Lawrence

**For a complete listing of research faculty and staff, see the Department of Pharmacology home page: <http://www.uic.edu/depts/mcph/>.**

## **Graduate Studies Coordinator, Room E403 MSB**

Cynthia Sanders, 355-3281; email to [cynsan@uic.edu](mailto:cynsan@uic.edu). The graduate studies coordinator is responsible for all the administrative aspects of the graduate program from applications and admissions to prelim exams, thesis defenses, graduation requirements, submission of petitions, transfer of credits, committee selection forms, etc. The coordinator also is responsible for organizing handling announcements for the student research forum. If you have questions not covered by this handbook, or to suggest additions and changes, contact Ms. Sanders.

## **Function of Departmental Office, Room E403 MSB, 312-996-7635**

The departmental office staff supplies administrative support for the instructional mission and research activities of the department. The office staff prepares lecture outlines and other materials for class use and provides administrative resources for the faculty. These services are available to all faculty involved in teaching and research programs.

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### Support Staff Responsibilities

Kathy Andrykowski  
Assistant to the Head

Academic appointments; university budget; grants management; administrative reports; consultations with staff concerning university policies and procedures regarding purchasing, travel, department inventory; processing of grant applications, budgetary matters; departmental liaison with university administrative, business, Affirmative Action, and human resources offices, establishes and implements policy for hiring and retaining international faculty, students, and visitors through the Office of International Services; assists the Executive Head in developing, implementing and evaluating Departmental administrative procedures; develops and implements in concert with the Executive Head, strategic planning policies to ensure the academic and fiscal success of the Department.

Aileen Baker  
Special Assistant to the Head

Responsible for the administrative duties of the Department Head. Serves as a liaison between faculty, staff, and students and the Department Head. Prioritizes work and coordinates meetings and conferences. Coordinates staff activities. Prepares and maintains confidential files and reports. Oversees major lab renovations and space allocation. Oversees IT resources

and support staff. Maintains departmental web site. Prepares departmental information regarding training grants. Coordinates submission of NIH progress reports. Coordinates faculty searches.

Amina Chavero  
Accounting Technician I

Reconciles PCard transactions and collects receipts. Manages the budget for some of Dr. Malik's accounts. Creates reports to PI's on their accounts. Balances accounts and reconcile ledgers. Create phone reports for each PI. Orders supplies for the main office. Package distribution. Key registration and distribution. Supervises the distribution of mail. Oversees the maintenance of core equipment. Coordinates work orders with physical plant or outside contractors for office/lab repairs, moves, maintenance problems, etc. Coordinates telecommunication requests for phone installations, changes, or repairs.

Chunfang Dai  
Director of Departmental Financial Affairs

Provide support to the Department Head to manage the health of the department finance and the financial perspectives the research grants.

Laura Foote  
Project Coordinator

Assists guest speakers with presentations and processes information for seminars including travel, schedules, student attendance, etc. Assists department members with flight arrangements. Trains staff/students on the use of the LCD projector and assists if needed with the setup of lectures and research forums. Departmental contact for the Environmental, Health and Safety Office. Maintains time records and inventory of research equipment. Prepares reimbursements and orders. Processes visa paperwork for international staff and faculty.

Charla Henry  
Visiting Project Coordinator

Assists Assistant to the Head with the processing of new and retained international faculty, staff, students and visitors; Processes AHA, DOD, and NIH grants; Consults with faculty, staff and visitors concerning University policies and procedures regarding purchasing, and the processing of grant applications and contracts; Acts as departmental liaison with other University administrative offices such as International Services, Research Services, and Human Resources; Assists Assistant to the Head in implementing departmental administrative procedures.

Cynthia Sanders  
Director of Program Development

Coordinates the administrative aspects of the graduate program. Coordinates NIH grant submissions for the department. Serves as REACH coordinator for the department assisting in computer hardware/software troubleshooting, purchasing and distributing appropriate software and licenses. Coordinates faculty searches. Administers research protocols of the Department Head.

## Departmental Committees

The following are lists of general departmental committees. Graduate students are encouraged to contact these committees with suggestions.

### *Graduate Committee*

R. Skidgel (Chair)

T. Guenther

J. O'Bryan

R. Ye

R. Minshall

### *Department Advisory Committee*

R. Skidgel (Chair)

D. Mehta

T. Guenther

X. Du

R. Ye

## Student Representatives for 2010-11

The *Graduate Student Council* representative is Brian Estevez. The *Student-Faculty* representatives are Alexander Garcia and Farnaz Bakhshi. Elections for 2011-2012 representatives will be held shortly after the start of the academic year.

## FACULTY RESEARCH INTERESTS

### **Marcelo Bonini, PhD (University of Sao Paulo)**

#### **Assistant Professor of Medicine**

#### **Section of Cardiology, and Pharmacology**

My research interests focus on the mechanisms and consequences of nitric oxide synthase (NOS) physiological and prolonged activation in health and disease. It is our currently working hypothesis that nitric oxide synthases are vulnerable checkpoints mediating physiological signaling through the controlled production of nitric oxide or oxidative stress depending on multiple factors which include substrate and cofactor availabilities and upstream kinase/phosphatase activity balance. Our current model is based on the investigation of the mechanisms through which nitroglycerin, a commonly used vasodilator, elicits vasodilation immediately after administration while inducing endothelial dysfunction upon continued use. Our results have demonstrated that nitric oxide synthase activation leads to the therapeutic effects observed in the clinic and indicated that failure in deactivating NOS may contribute to dysfunction. Our laboratory is prepared to support research involving an array of biochemical and biophysical techniques which include HPLC, Western Blots, ELISA, electron paramagnetic resonance (EPR), cell cultures and animal models as well as chemiluminescent detection of nitric oxide and immuno-spin trapping.

### **Graeme K. Carnegie, PhD (University of Dundee, UK)**

#### **Assistant Professor**

#### **Coordination of cell signaling by protein targeting and scaffolding.**

Research in my laboratory is based on understanding how signal transduction is coordinated by scaffolding and subcellular targeting of proteins to regulate physiological functions.

Specifically, we study scaffolding complexes mediated by A-Kinase Anchoring Proteins. AKAPs are a diverse family of scaffold proteins that form multi-protein complexes, integrating cAMP-signaling with protein kinases, phosphatases and other effector proteins. Many AKAPs have been characterized in

the heart, where they play a critical role in modulating cardiac function.

We are currently focusing on AKAP-Lbc (also known as AKAP13) in cardiac cellular function and pathogenesis. AKAP-Lbc coordinates signal transduction through multiple protein kinases and plays a role in pathological cardiac hypertrophy, which is often a major component underlying cardiovascular disease.

Using *in vivo* mouse models, biochemistry, molecular biology, and live cell-imaging techniques, we are dissecting signaling through AKAP-Lbc. Our aim is to determine how the AKAP-Lbc complex coordinates multiple signals that may contribute to cardiovascular disease.

**Jaehyung (Gus) Cho (Ph.D., University of Wisconsin-Madison)  
Assistant Professor**

The research interest of my laboratory is to understand the molecular mechanisms of thrombo-inflammatory diseases. We are currently focusing on how protein disulfide isomerase (PDI) regulates integrin-mediated platelet and leukocyte functions. These studies are being performed mainly using *in vivo* multi-fluorescence intravital microscopy using various knockout mice. A better understanding of the role of platelets and leukocytes in thrombo-inflammatory diseases could lead to the development of effective therapeutics to prevent and treat vascular diseases.

**Oscar Colamonici, M.D. (University of Uruguay)  
Associate Professor**

The main research focus of our lab has centered on the role of the mammalian orthologs of the *Drosophila* dREAM complex in cell cycle regulation. The two projects currently underway can be summarized as follows.

**1) Regulation of G1 by Mip/LIN-9**

Understanding the mechanisms that govern cell cycle progression is important for the development of novel therapeutic agents against cancer. The G1 phase is a critical crossroad where positive and negative regulatory signals converge to control cell cycle progression. The family of pocket proteins is responsible for restricting cell cycle progression via the formation of repressor complexes with E2F and DP family members, which result in the inhibition of E2F target genes. We cloned a novel gene, originally named BARA, currently termed human Mip/LIN-9, which regulates cell cycle progression. Our studies demonstrate that deletion of the first 84 amino acids of Mip/LIN-9 (Mip/LIN-9<sup>Δ84</sup>) corrects the CDK4 null phenotype. Therefore, Mip/LIN-9, like the pocket proteins pRB, p107 and p130, is negatively regulated by CDK4. Interestingly, the correction of the CDK4 null phenotype is accompanied by a restoration of the expression of genes such as E2F1, E2F3, and cyclin E suggesting that Mip/LIN-9 participates in the regulation of E2F target genes required for the G1/S transition. This is further supported by the finding that Mip/LIN-9 interacts with two members of the pocket family, p107 and p130. The objectives of this project are: 1) To characterize the mechanism that leads to the correction of the CDK4 null phenotype by the mutation  $\Delta 84$  of Mip/LIN-9. 2) To test the hypothesis that Mip/LIN-9 is part of the transcriptional repressor complex formed by p107,130/E2F4,5/DPs and that its interaction with other members of the complex is required for the regulation of the expression of E2F target genes responsible for cell cycle progression.

**2) Regulation of S phase and mitosis by Mip/LIN-9.**

In *Drosophila*, the homolog of Mip/LIN-9, Mip130, is part of a large complex termed dREAM (drosophila RB, E2F and Myb) that includes pocket proteins, repressor forms of E2F, B-Myb and B-Myb-interacting proteins termed Mip(s). This complex inhibits transcription of specific genes and duplication of specific genomic regions. Our data suggest that the mammalian equivalent of Mip130, Mip/LIN-9, forms a complex with pocket proteins, E2Fs and B-Myb; however, unlike the *Drosophila* counterpart, not all proteins are in the same complex simultaneously. For example, Mip/LIN-9 interacts with p107, p130 and E2F4 in G0 and early G1, and with B-Myb in late G1 and S phase. Moreover, while the complex that Mip/LIN-9 forms with E2F4 and p107 or p130 has a repressor effect, the interaction with B-Myb is responsible for the induction of critical S-phase and mitotic genes such as cyclin A, cyclin B and CDK1. Additionally, we are characterizing the role of mammalian Mip40/LIN-37 and Mip120/LIN-54 whose orthologs are also part of the dREAM and DRM complexes in *Drosophila* and *C. elegans*, respectively.

**Xiaoping Du, M.D., Ph.D. (University of Sydney)**  
**Professor**

Research interests of this laboratory are in the field of thrombosis, hemostasis, and vascular biology. Specifically, we study cell adhesion and signaling, including: 1) signaling mechanisms of platelet adhesion receptor, glycoprotein Ib-IX. 2) signaling mechanisms of integrins, particularly beta 3 integrins. 3) the roles of GTP binding proteins in platelet activation, and 4) the role of nitric oxide-cGMP-dependent signaling pathway in regulating platelet function.

**Tohru Fukai, M.D., Ph.D. (Kyushu University School of Medicine, Japan)**  
**Associate Professor**

Oxidative stress and essential nutrient Copper (Cu) plays a key role in the pathogenesis of various cardiovascular diseases, and postnatal neovascularization. Major focus of our research is extracellular superoxide dismutase (ecSOD) and its regulators Cu transport proteins. The ecSOD is one of the major copper containing antioxidant enzymes in the vasculature, and plays an important role in regulating blood pressure, neovascularization, and endothelial function by preventing oxidative inactivation of NO. Cu transport proteins, including antioxidant-1 (Atox1) and Copper-transporting ATPase ATP7A, are a key regulator of ecSOD activity and expression as well as growth factor signaling. Thus, the long term goal of our lab is to determine the role of Cu transport proteins as well as ecSOD to define their functional relationships in oxidative stress-dependent cardiovascular disease.

**Guochang Hu, M.D., Ph.D. (China Medical University)**  
**Assistant Professor of Pharmacology and Anesthesiology**

My Laboratory focuses on the molecular and cellular mechanisms of acute lung injury/acute respiratory distress syndrome (ALI/ARDS). The bacterial endotoxin (lipopolysaccharide, LPS) can trigger a systemic hyper-inflammatory response that subsequently leads to multiple organ dysfunction syndrome. LPS binding to toll-like receptor 4 (TLR4) induces the activation of mitogen-activated protein kinase (MAPK) and nuclear factor- $\kappa$ B (NF- $\kappa$ B) resulting in production of pro-inflammatory cytokines. When this production becomes uncontrolled and excessive, it leads to the development of septic shock. The objectives of our current project are to define the anti-inflammatory role of adherens junction protein p120-catenin, determine the mechanism of p120-catenin degradation induced by LPS, and to explore the possibility that p120-catenin interferes with the TLR4-activated signaling pathway to mitigate lung inflammatory injury.

Another research interest is the molecular mechanisms regulating vascular endothelial permeability. An important function of the endothelium is to regulate the transport of liquid and solutes across the semi-permeable vascular endothelial barrier. Two cellular pathways have been identified controlling endothelial barrier function. The normally restrictive *paracellular pathway*, which can become "leaky" during inflammation when gaps are induced between endothelial cells at the level of adherens and tight junctional complexes, and the *transcellular pathway*, which transports plasma proteins the size of albumin via transcytosis in vesicle carriers originating from cell surface caveolae. We are interested in elucidating the signaling mechanisms that regulate paracellular and transcellular endothelial permeability pathways in response to inflammatory insults.

**Yulia Komarova (Moscow State University)**  
**Assistant Professor**

The endothelium functions as a semi-permeable barrier between the blood plasma and interstitium thus regulating tissue fluid homeostasis. Impairment of the endothelial barrier is a key early event in the development of Adult Respiratory Distress Syndrome (ARDS). This condition is clinically manifested as a severe loss of gas exchange capacity and hypoxemia that is often fatal.

The focus of my research is on the cross-talk between microtubule cytoskeleton and VE-cadherin-mediated adhesions in lung microvascular endothelial cells. Dynamic interaction between cytoskeleton

and adherens junctions is known to be important for maintenance of basal endothelial barrier permeability and underlies changes in endothelial permeability in response to different mediators. I am investigating the molecular and signaling mechanisms regulating microtubule cytoskeleton downstream of adherens junction and how changes in microtubule dynamics affect integrity of endothelial monolayer in response to extracellular stimuli. By establishing how MTs mediate increased lung vascular permeability we will be in a position to define novel therapeutic targets to treat ARDS.

**Tohru Kozasa, M.D., Ph.D. (University of Tokyo)**  
**Associate Professor**

Our laboratory has been conducting biochemical investigations on G protein mediated signal transduction pathways. The main theme is to understand the regulatory mechanism of activation of Rho family GTPases (Rho, Rac, Cdc42) by heterotrimeric G proteins. Rho family GTPases are involved in a variety of cellular functions mainly by controlling the organization of actin cytoskeleton. We have recently demonstrated that Galpha12 and Galpha13, whose effectors were previously unknown, interact with and regulate the activity of a novel Rho specific GEF (guanine nucleotide exchange factor), p115RhoGEF. This result was the first demonstration of the biochemical link between Rho family monomeric GTPases and heterotrimeric G proteins. We will characterize the regulation of p115RhoGEF by Galpha12/G 13 in detail using biochemical assays with purified components, X-ray crystallography analysis, and also cell-based Rho activation assays. The involvement of this signaling pathway in cellular functions such as neurite extension, angiogenesis, chemotaxis, or cell-cell adhesion will be pursued in future. We are also analyzing in vivo function of this pathway using *C. elegans* as a model animal. We have recently identified a brain specific effector candidate GRIN1 for Galphao. Galphao is extremely abundant protein in brain but its physiological function is unknown. Both Galphao and GRIN1 are highly enriched at growth cone of neurons. In addition, we demonstrated that activation of Galphao-GRIN1 pathway stimulates neurite formation in cultured cells. We plan to investigate the physiological significance of this signaling pathway in brain function.

**Guy C. Le Breton, Ph.D. (University of Chicago)**  
**Professor**

In order to study thromboxane (TXA<sub>2</sub>)-mediated human blood platelet signal transduction pathways, our research program utilizes a wide range of chemical, biochemical, immunological, pharmacological and molecular biology techniques. The first aim of this project, to map the thromboxane receptor (TPR) ligand binding domain, is based on our hypothesis that signal transduction through TPRs is initiated by TXA<sub>2</sub> interaction with extracellular regions of the receptor protein. Support for this hypothesis was provided by our identification of a ligand coordination site in the second extracellular loop of human TPRs (Turek et al., JBC, 2002) and our recent characterization of specific amino acids within this domain (Khasawneh et al., JBC, 2006). A separate aim is to investigate cross-signaling between platelet G-protein-coupled receptors (GPCRs). This work is based on our hypothesis that receptor-G protein (GPCR-GP) complex formation derives from the principles of mass action, and that this principle defines, modulates and prioritizes GPCR signaling in both cellular development and disease (Djellas et al., PNAS, 1998; Djellas et al., Biochemical Pharmacol., 2000; Huang et al., Cell Signaling, 2003; Huang, et al. Cell Signaling 2006). An additional aim investigates the molecular and functional consequences of G protein Switch Region inhibition, particularly as it relates to G<sub>13</sub> signaling (Djellas et al., JBC 1999). Our hypothesis is that phosphorylation of the conformationally sensitive Switch 1 Region of G<sub>13</sub> plays an important role in modulating signaling through the G<sub>13</sub> pathway (Manganello et al., JBC 1999). We have provided evidence for a PKA phosphorylation site within this region at Thr203 of G<sub>13</sub> (Manganello. et al., JBC 2003), and recent experiments have identified specific peptide sequences that interfere with Switch Region 1 signaling (Huang, et al., JBC, 2007). The last aim of this project investigates the cellular signaling of a novel class of lipids called the isoprostanes. In this connection, we propose that isoprostanes signal in human platelets through two opposing pathways: one linked to TPRs; and the other linked to a novel receptor. This hypothesis derives from two recent findings (Khasawneh, et al., Biochemical Pharmacol., 2008). Firstly, there is a significant inhibitory

component of isoprostane signaling that is only revealed when TPR signaling is blocked. Secondly, isoprostanes interact with platelets at two distinct binding sites, one stimulatory site that is represented by TPRs, and one inhibitory site that is presently unidentified. While our preliminary results have linked this inhibitory site to increased cAMP levels, the putative receptor involved in this increase is currently unknown. Consequently, these studies will identify and characterize this unidentified isoprostane receptor, and examine its involvement in platelet function/thrombus formation *in vivo*.

A separate research program is aimed at studying the involvement of TPR signaling in the nervous system. In this regard, we have previously demonstrated a high density of functional TPRs in both oligodendrocytes and Schwann cells, the cells responsible for nervous system myelination (Borg, et al., JBC, 1994; Blackman et al., JBC 1998; Muja et al., J. of Neurochemistry 2001). In addition, we have obtained exciting new evidence demonstrating that TPR activation promotes oligodendrocyte (OLG) proliferation, prolongs OLG survival (Huang, et al., Cell Signaling, 2004; Lin, et al., J Neurochemistry, 2005), and stimulates myelin basic protein (MBP) synthesis by increased transcription from the MBP promoter. Most recently, our results have established that TXA<sub>2</sub> is synthesized at all stages of OLG development, and that TPR localization shifts from the plasma membrane to the nuclear compartment during development (Ramamurthy, et al., J. Neuroscience Res., 2006). These results provide the first documentation that there are separate TPR signaling mechanisms in OLGs that collectively modulate viability and myelin component expression. Based on these findings we propose that TPRs signal OLG nuclear events involved in OLG development and myelin gene transcription. To test this hypothesis, we will: 1. Investigate TPR modulation of OLG development and myelination *in vivo* by use of a tamoxifen(TAM)-inducible TPR knockout mouse; 2. Define the *in vivo* involvement of TPR signaling in OLG development, function and survival during disease and stress using two myelin disease models (EAE and Cuprizone-induced demyelination); and 3. Define the mechanisms by TPR signaling modulates OLG development and myelin component synthesis. Collectively, these studies will make fundamental contributions to understanding the mechanisms involved in myelin elaboration/destruction and, in turn, lead to novel approaches to the treatment of multiple sclerosis.

**Asrar B. Malik, Ph.D. (University of Toronto)**  
**Schweppe Family Distinguished Professor and Department Head**

A major interest of the laboratory is to understand the regulation of the barrier properties of endothelial and epithelial cells. We are studying the events occurring at the receptor level and the signaling pathways that regulate the barrier function of these monolayers. As thrombin has been shown to increase endothelial permeability, we use this agonist to study how the activation of its proteolytically cleaved receptor leads to the increase in permeability. Researchers have localized the domains of the receptor involved in activation and in shutting off endothelial cell signaling. Another approach taken is to clone a dominant negative form of the receptor and use it to inhibit thrombin receptor activation. These studies pursue the cellular effector pathway's increasing permeability to understand how the activation of the signaling pathways mobilizes these effectors (i.e., actin-myosin motor, cadherin-catenin complex and the intermediate cytoskeletal filaments). From these studies, our research has expanded to include the use of stem and other progenitor cells in the re-annealing and revascularization of the endothelial barrier during such conditions as Acute Respiratory Distress Syndrome.

Another goal of the lab is to develop and to test novel strategies for drug and gene delivery. We are interested in targeting specifically the cells of the vessel wall, which are critical in the pathogenesis of variety of inflammatory diseases, atherosclerosis and cancer metastasis. The intent of this strategy is to prevent, in a specific manner, the expression of endothelial adhesion molecules. Among the approaches being studied include selective expression using inducible promoters in order to target the expression of "anti-adhesive" proteins in endothelial cells. We are also developing non-viral means of gene delivery to transduce endothelial proteins of interest. The approaches taken involve molecular biology as well as physiological monitoring in experimental models.

The lab is also pursuing studies in the use of stem cells including endothelial progenitor cells, to repair vascular injury. We are characterizing these cells and assessing their growth characteristics as well as

developing novel markers for their identification. Our objectives are to develop novel cell based therapy to prevent microvascular injury that is a characteristic feature of multiple diseases such as atherosclerosis, lung inflammatory injury, and ischemia-perfusion vascular injury.

A final area of study in our laboratory is to study the expression of the adhesion molecule ICAM-1 at the level of gene transcription. In particular, we are interested in how certain cytokines and oxidants induce the expression of the ICAM-1 gene at the level of its promoter, the intra-cellular signaling pathways regulating ICAM-1 expression, and how gene activation is regulated by the redox state of the cell. We have identified an element on the promoter that is activated by hydrogen peroxide. Activated transcription factors bind in a complex manner to this element and initiate ICAM-1 transcription. Our objective is to understand the genetic basis of ICAM-1 expression, and then to develop strategies for controlling the expression of this adhesion molecule and to regulate leukocyte trafficking across the vascular endothelium.

**Dolly Mehta, Ph.D. (Dehli University)**  
**Associate Professor**

Acute Respiratory Distress Syndrome (ARDS) is a devastating, often fatal, inflammatory lung disease that usually occurs in conjunction with a catastrophic medical condition, such as pneumonia, shock, sepsis, and trauma. ARDS affects approximately 150,000 patients each year, and results in 40% mortality. No specific therapies currently exist for ARDS. The integrity of the endothelial exchange barrier is a key factor in lung homeostasis and normal cardiovascular function. Increased endothelial permeability in lungs leads to the leakage of fluid and macromolecules, and if not resolved, to ARDS. Thus, our overall goal has been identifying the signaling "switches" (i) that induce endothelial cell contraction and compromise endothelial barrier function, and (ii) those that turn off endothelial contraction, promoting barrier repair.

Specific Projects in the lab include:

- a) Investigate the role of transient receptor potential channel (TRPC) primarily TRPC6 and TRPC1, which mediates Ca<sup>2+</sup> entry in endothelial cells, in inducing cytoskeletal re-organization and subsequently the loss of endothelial barrier function.
- b) Determine the role of GDI-1 in regulating RhoGTPase activity and the integrity of endothelium.
- c) Address the novel role of endothelial focal adhesion kinase (FAK) in turning-off endothelial cell contraction, thereby restoring endothelial barrier.
- d) Determine that sphingosine kinase 1 (SPHK1) is a potential key regulatory switch that antagonizes thrombin-induced increase in endothelial permeability by generating S1P

We use genetic mouse models and deliver mutant constructs or siRNA to down regulate identified genes in endothelial cells and mouse lungs to assess the role of above described signaling switches in regulating endothelial barrier function. These studies are accompanied with state-of-the-art cell imaging techniques. We hope that undertaken projects will be potentially helpful in developing therapeutics against ARDS.

**Richard D. Minshall, Ph.D., (University of Illinois, Chicago)**  
**Associate Professor of Pharmacology and Anesthesiology**

Using genetic *in vivo* and *in vitro* approaches, disease models, and human tissues, we are determining whether caveolin-1 expression level and post-translational modification participates in the regulation of lung vascular homeostasis and in the etiology of lung diseases. Our goal is to determine whether this basic information can be used to develop novel therapeutic approaches for treating inflammatory and remodeling lung diseases. Current research projects are characterizing the role of caveolin-1 in the regulation of 1) transcellular vesicular transport and lung fluid homeostasis, 2) leukocyte recruitment and transmigration initiated by cell surface adhesion molecule activation, 3) lung microvascular endothelial cell differentiation and angiogenesis, and 4) distal lung epithelial progenitor cell differentiation and lung development. In these studies, we have shown that caveolin-1 plays an essential role in the regulation of Src, dynamin-2, and eNOS signaling, and that downstream phosphorylation and nitrosylation events

regulate caveolin-1 expression, caveolae-mediated endocytosis, angiogenesis, vascular tone, and inflammation. Furthermore, endothelial cell function and inflammation-evoked endothelial hyperpermeability measured in *Cav1*<sup>-/-</sup>, *eNOS*<sup>-/-</sup>, and double knockout mice as well as isolated lung microvascular endothelial cells and expression systems is revealing feed-back and feed-forward mechanisms of caveolin-1 regulated eNOS and Src signaling. For example, we have shown that NO-mediated Src activation provides a negative feedback mechanism to inactivate eNOS and Src mediated by phospho-caveolin-1 dependent sequestration of eNOS as well as recruitment of Csk, the Src inactivating kinase. The clinical importance of these observations is suggested by studies which link reduced Cav-1 expression to eNOS-dependent ROS production, sustained Src activation, disruption of endothelial monolayer integrity, aberrant angiogenesis, and increased pulmonary vascular resistance associated with pulmonary arterial hypertension. In a similar manner, we have observed that ICAM-1 activation-dependent NO and O<sub>2</sub><sup>-</sup> production induces Src-dependent caveolin-1 and dynamin-2 phosphorylation, caveolae-mediated transcellular protein transport, and leukocyte transmigration. Thus, Cav-1 expression, via regulation of eNOS and Src signaling, is an important determinant of host defense and inflammation-induced vascular injury. New investigations are defining the role of caveolin-1 in lung vascular and airway development and repair by examining isolated mouse lung endothelial cell and alveolar epithelial progenitor cell growth and differentiation *in vitro* and *in vivo*.

**Viswanathan Natarajan, PhD (Indian Institute of Science)**  
**Professor of Pharmacology & Medicine**  
**Co-Director, Institute for Personalized Respiratory Medicine**

My laboratory has been investigating for over 25 years the role of reactive oxygen species (ROS) and bioactive lipids in vascular endothelial signaling, injury and barrier integrity. ROS have been implicated in the pathophysiology of several respiratory diseases including ARDS, COPD, pulmonary hypertension and bronchopulmonary dysplasia and our current primary focus is on the role and regulation of NADPH Oxidase and NOX proteins in hyperoxia- and sepsis-induced lung injury. We were the first to demonstrate that sphingosine-1-phosphate (S1P) is an agonist in endothelial cell signal transduction and S1P is the most potent angiogenic naturally occurring bioactive lipid that is present in plasma and tissues. My laboratory has been studying mechanisms of generation of intracellular S1P mediated by sphingosine kinases and degradation catalyzed by lipid phosphate phosphatases and S1P lyase in the endothelium and S1P lyase as a novel target of sepsis-mediated lung injury. Our investigations suggest a role of intracellular S1P in lung inflammation, injury, cell motility and NADPH Oxidase dependent ROS production. More recently, we have been investigating the role of HATS and HDACs in Mesothelioma and potential regulation of HATS/HDACs by sphingosine kinases and S1P lyase. These ongoing projects involve basic and translational research to develop novel therapeutic strategies and targets to limit the adverse effects of inflammatory lung injury.

**John P. O'Bryan, Ph.D. (University of North Carolina at Chapel Hill)**  
**Associate Professor**

The research interests of my laboratory are focused on the role of scaffolding proteins in regulating signal transduction pathways particularly from receptor tyrosine kinases. Scaffolding proteins consist primarily of modular protein interaction domains that promote specific protein: protein interactions within cells. This class of molecules serves to assemble multi-protein complexes that mediate the temporal and spatial activation of various pathways. I am particularly interested in the role of the intersectin scaffolding protein. Intersectin possesses a unique modular structure that allows it to interface with many pathways. Although this protein was initially described as a regulator of the endocytic pathway, we have discovered that intersectin regulates the activation of a number of signal transduction pathways. For example, intersectin activates the c-Jun N-terminal kinase pathway, an important modulator of cell growth and apoptosis. In addition, we have discovered that intersectin overexpression promotes the oncogenic transformation of cells. And finally, we have uncovered an important role for intersectin in the function of receptor tyrosine kinases, an important class of receptors involved in cell growth, differentiation and development. Abrogation of receptor tyrosine kinase pathways leads to a variety of pathological conditions including cancer. Our findings on intersectin are particularly

interesting given that the intersectin gene is localized on human chromosome 21 and thus present in an extra copy in Down's Syndrome patients (Trisomy 21). Indeed, intersectin expression is elevated in the brains of Down's Syndrome patients as well as in a mouse model for Down's Syndrome. These observations suggest a possible involvement of intersectin in the sequelae of Down's Syndrome.

The research projects in my laboratory are aimed at understanding the biochemical and physiological role of this evolutionarily conserved scaffolding protein. We utilize a wide range of approaches including molecular biology, cell biology, biochemistry and animal models to understand intersectin's role in the cell. Current projects are focused on the following areas:

1. *Determining the mechanism by which ITSN stimulates mitogenic signaling pathways.* We have identified several signaling pathways that are regulated by intersectin. Our current goal is to determine the precise mechanisms by which intersectin regulates these pathways as well as the functional consequences to this regulation.

2. *Determining the role of ITSN in ubiquitination.* We have recently discovered that intersectin serves as a scaffold for the recruitment of several E3 ubiquitin ligases, enzymes that catalyze the covalent attachment of ubiquitin to proteins. We are now focusing on determining the mechanisms by which intersectin regulates the activities of these ligases.

3. *Determining the role of ITSN in development and disease.* We have begun to explore the importance of ITSN during development through the use of transgenic and knockout animal models. Given the pathways that intersectin regulates as well its association with Down's Syndrome and oncogenic transformation, we have developed regulated intersectin transgenic animals for exploring the physiological consequences to intersectin overexpression in specific tissues. In addition, we are developing animals in which we specifically down-regulate intersectin expression through the use of stable silencing RNA. These animals will provide important *in vivo* models for understanding intersectin function in both normal and disease processes.

**Changwon Park, Ph.D. (Washington University School of Medicine, St. Louis)  
Assistant Professor**

The main interest of my lab is to study the biology of vascular endothelial cells. With mouse genetics and embryonic stem (ES) cell differentiation system, we are currently investigating molecular mechanisms governing 1) the generation/differentiation of endothelial cell (progenitors) in developing embryos and 2) the process of neovascularization in pathophysiologic conditions. We are also interested in cell reprogramming.

**Jalees Rehman, MD (Technische Universität München)  
Associate Professor of Medicine and Pharmacology**

Regenerative stem cells and progenitor cells in the cardiovascular system may lead to exciting novel therapies directed at treating cardiovascular diseases, such as congestive heart failure, cardiomyopathy and severe coronary artery disease. While some preliminary studies using novel cell-based therapies in patients have been promising, these therapies are not yet ready for a routine usage in patients. One key obstacle to the clinical use of stem cells and progenitor cells in cardiovascular disease is the fact that we know so little about the actual biology of stem and progenitor cells in the cardiovascular system. Understanding the mechanisms by which stem and progenitor cells help repair and regenerate the cardiovascular system would allow us to develop very efficient and safe therapies that our research laboratory is therefore studying three core areas of stem and progenitor cell biology:

**The Role of Endothelial Progenitor Cells (EPCs) in Enabling Vascular Repair and Angiogenesis:**  
The discovery of circulating endothelial progenitor cells has suggested that the endothelium may undergo endogenous repair following injury by such circulating EPCs. Our research has helped define and characterize the nature of EPCs by demonstrating that that at least two distinct types of EPCs can

be found in the blood: Highly proliferative EPCs that are resistant to cellular senescence because of low expression levels of the senescence mediator p16INK4A and minimally proliferative macrophage-like EPCs that exert their protective effects by secreting angiogenic growth factors or lipid mediators such as endocannabinoids. We are currently exploring the question, whether the adult vasculature contains a heterogeneous population of vascular endothelial cells, some of which may be immature EPCs and repair the vessel wall in response to stress or injury.

**Mitochondrial metabolism and Reactive Oxygen Species (ROS) as regulators of stem cell differentiation and self-renewal:** Mitochondria have been traditionally seen as a major powerhouse that generates ATP, however recent studies show that mitochondria are critical regulators of cell death and cell proliferation, in part via the release of Reactive Oxygen Species (ROS), which can act as signaling molecules. Our most recent data suggest that mitochondrial activity also regulates the differentiation of both embryonic and adult stem cells, and we are currently identifying the specific pathways by which mitochondria exert this regulator effect.

**The mechanisms underlying the protective role of Mesenchymal Stem Cells (MSCs):** Adult MSCs have generated a large amount of interest in their therapeutic potential in cardiovascular disease. Unfortunately, transplanted adult MSCs demonstrate only minimal engraftment and survival and this may limit their therapeutic use. In this project, we are specifically studying the paracrine factors released by MSCs and also improve the engraftment and survival of MSCs. It appears that they do not necessarily differentiate into endothelial cells or cardiomyocytes, but create a microenvironment that permits cardiovascular repair and regeneration.

**Miodrag Radulovacki, M.D., Ph.D. (University of Belgrade Medical School)  
Professor**

Pharmacology of sleep and sleep-related breathing disorders. Role of serotonin in the mechanisms of sleep apnea (cessation of respiration). Sleep apnea syndrome affects at least 3%-5% of adult population in the US and we and others, have shown that adult rats also exhibit apneas during all stages of sleep. It is now well established that the prevalence of sleep-related apnea is dramatically elevated in the elderly ranging from 28%-67% and we are studying the phenomenon using the rats of all ages as animal model of sleep apnea.

Our studies using the rat model of sleep apnea and in patients with the sleep apnea provided new data about the serotonin mechanisms underlying that breathing disorder. Since there is no pharmacological treatment of sleep apnea syndrome, our research opened avenues for the development of a therapeutic approach to sleep-related apneas.

**Randal A. Skidgel, Ph.D. (University of California at San Diego)  
Professor and Vice Director, Laboratory of Peptide Research**

Sepsis, a leading cause of acute lung injury, causes pulmonary inflammation and increased capillary endothelial permeability and is a potent stimulus for inducible nitric oxide synthase (iNOS) expression. iNOS generates high output nitric oxide (NO) that plays important roles in regulating lung vascular permeability. Although iNOS is thought to be primarily regulated at the level of expression, we have discovered a novel GPCR-mediated signaling pathway that acutely activates iNOS in cytokine-stimulated human lung microvascular endothelial cells (HLMVECs). We are currently investigating these signaling pathways. We have found that high output NO itself has a protective effect on the endothelial barrier and we are investigating the role of small GTPases Rac, Rho and CDC42 in this response. In contrast, in the presence of other inflammatory mediators such as thrombin or superoxide generation, activation of iNOS results in exacerbation of barrier disruption, due to generation of peroxynitrite. We are also investigating a novel signaling pathway activated by the bradykinin B2 receptor that stimulates prolonged, high-output NO via eNOS in cytokine-activated HLMVECs. These studies will identify novel mechanisms by which lung microvascular endothelial cells under inflammatory conditions can generate high-output NO as *autocrine* and *paracrine* signals to alter

endothelial permeability. It will also allow identification of potential targets for therapeutic intervention to improve endothelial barrier function in conditions such as septic shock and acute respiratory distress syndrome (ARDS).

In another set of studies, we are seeking to understand the important roles of regulatory carboxypeptidases in physiological and pathological processes. We have discovered an important protein-protein interaction between carboxypeptidase M (CPM) and the B1 kinin receptor that allows efficient delivery of des-Arg-kinin agonist generated by CPM to the receptor. Recent findings indicate that binding of bradykinin or other non-kinin substrates to CPM can indirectly activate the B1 receptor by inducing a conformational change via protein-protein interaction on the cell surface. This novel way of regulating GPCR signaling could be exploited to develop drugs to alter CPM/B1R interaction and thereby regulate kinin signaling that plays important roles in inflammatory processes and cardiovascular function.

**Chinnaswamy Tirupathi, Ph.D. (University of Madras)  
Associate Professor**

My research interest focused on studying the mechanism of activation of endothelial cells by thrombin. The consequence of activation of endothelial cells by thrombin leads to increase in endothelial permeability and polymorphonuclear leukocyte (PMN) adhesion-mediated vascular injury. Thrombin-induced increase in cytosolic  $Ca^{2+}$  is critical in the mechanism of increased endothelial permeability and PMN adhesion-mediated vascular injury. Thrombin-induced increase in cytosolic  $Ca^{2+}$  is associated with intracellular store  $Ca^{2+}$  depletion as well as  $Ca^{2+}$  influx from extracellular medium. Our recent findings suggest that transient receptor potential (TRP) channels expressed in endothelial cells are activated by thrombin to cause  $Ca^{2+}$  influx. Our studies further showed that TRPC4, a predominant TRP channel isoform expressed in mouse lung endothelial cells and deletion of TRPC4 in mouse, impaired thrombin-induced increase in lung microvascular permeability. Moreover, we showed that human vascular endothelial cells predominantly express TRPC1 isoform and it is an essential component of store-operated cation channels. We are currently investing how these channels expression in endothelial cells is regulated at the transcriptional level by the pro-inflammatory mediators such as tumor necrosis factor- $\alpha$ , thrombin, and oxidants. We are also focused to address how  $Ca^{2+}$  influx signaling in endothelial cells regulates transcription factor nuclear factor  $\kappa$ B (NF- $\kappa$ B) activation, gene expression, and PMN adhesion-mediated vascular injury.

**Masuko Ushio-Fukai, Ph.D., F.A.H.A. (Kyushu University, Fukuoka, Japan)  
Associate Professor**

Neovascularization is important repair process in response to ischemic injury and is involved in various pathophysiologicals such as ischemic heart and limb diseases, atherosclerosis and cancer.. This process is dependent on angiogenesis (formation of new capillaries from pre-existing vessels) and vasculogenesis (*de novo* new vessel formation through mobilization of endothelial progenitor cells (EPCs) from bone marrow (BM) and their recruitment to the ischemic sites). Our laboratory is the first to demonstrate that reactive oxygen species (ROS) derived from NADPH oxidase play a critical role in VEGF signaling in endothelial cells as well as ischemia-induced angiogenesis *in vivo*. Moreover, our recent studies using *Nox2<sup>-/-</sup>* mice indicate that NADPH oxidase-derived ROS are also involved in EPC mobilization from BM, homing and angiogenic capacity of BM stem/progenitor cells, thereby promoting revascularization in response to tissue ischemia. The long term goal of our lab is *to determine the molecular mechanism by which ROS derived from NADPH oxidase and mitochondria are involved in postnatal angiogenesis and vasculogenesis in physiological and pathological conditions such as diabetes and atherosclerosis*. Most recently, we are also investigating redox signaling mechanisms of human embryonic stem cell self-renewal and differentiation into endothelial cells.

**Kishore K. Wary, Ph.D. (North Eastern Hill University, Shillong, India)  
Assistant Professor**

The primary scientific focus of our laboratory is directed towards gaining an understanding of the molecular and transcriptional mechanisms that drive cell specification and differentiation of the endothelial cells. These NIH and AHA funded research efforts are centered on Lipid phosphate phosphatase-3 (LPP3) and NANOG and KLF4, in relation to neovascularization and regenerative medicine. The long-term translational research goal of our laboratory is to identify how defects in critical control circuits lead to the progression to unwanted angiogenesis which may aid in the development of novel therapeutic approaches for cardiovascular disease and stroke, acute lung injury and cancer.

**Jingsong Xu, Ph.D., (University of Southern California)  
Assistant Professor of Pharmacology and Dermatology**

Cell migration is essential for such physiological and pathological processes as embryonic development, neurite guidance, host defense, and tumor invasion. Despite their diversity of morphology and function, different migratory cells share a conserved set of intracellular signals to guide cell migration. Our long-term goal is to understand how cell migration is regulated on the molecular level and to seek new therapeutic targets and strategies for treating diseases related to cell migration. In particular, we plan to analyze signaling pathways that govern the cytoskeletal assemblies required for two key cellular responses during migration: polarization and directional sensing.

**Richard Ye, M.D., (Shanghai Second Medical University); Ph.D. (Washington University, St. Louis)  
Professor**

My laboratory is investigating how phagocytic leukocytes respond to environmental stimuli with activation of special cellular functions. These include the abilities of phagocytes to move towards the site of infection (chemotaxis), to engulf bacteria (phagocytosis), to produce reactive oxygen species (NADPH oxidase activation) and to release enzymes (degranulation). These functions are essential for the elimination of invading microbes, but can also contribute to inflammation.

Genetic and clinical evidence has shown that failure for phagocytes to produce superoxide is a cause of immunodeficiency, whereas inappropriate activation of phagocytes can lead to tissue injury and inflammatory disorders. We are investigating the mechanisms used by phagocytes to regulate the assembly of NADPH oxidase complex. A better understanding of the regulatory mechanisms will help to prevent oxidant-mediated tissue injury and promote superoxide production when challenged by pathogenic microbes.

Using immunopharmacological approaches, we are investigating how cell surface receptors transduce signals for the activation of a multitude of cellular activities. G protein-coupled receptors (GPCRs) constitute a large family of cell surface receptors that are frequent targets of therapeutic agents. Our laboratory is interested in GPCRs of the immune system, namely those that mediate phagocyte activation. We have developed methods to screen for small, synthetic ligands for a group of GPCRs, and hope to explore the therapeutic value of these novel agents. Our long-term goal is to apply our understanding of the cellular mechanisms of phagocyte activation to therapeutic intervention of infectious and inflammatory diseases.

**Jason X.-J. Yuan, M.D. (Suzhou Medical College, Suzhou), Ph.D. (Peking Union Medical College, Beijing & University of Maryland, Baltimore)  
*Professor of Medicine and Pharmacology  
Director, Pulmonary Hypertension Research Program, Institute for Personalized Respiratory Medicine***

The overall research interest of Dr. Yuan's laboratory is vascular physiology, electrophysiology and pathogenic mechanisms of pulmonary vascular disease, with particular emphasis on *i*) the regulation of excitation-contraction coupling and  $Ca^{2+}$  signaling in vascular smooth muscle, *ii*) the transcriptional and

functional regulation of ion channels ( $K^+$ ,  $Ca^{2+}$  and  $Cl^-$  channels) in smooth muscle and endothelial cells, *iii*) the cellular and molecular mechanisms of hypoxic pulmonary vasoconstriction, *iv*) the pathogenic and therapeutic mechanisms of idiopathic and thromboembolic pulmonary hypertension, and *v*) the functional role of ion channels in stem cell proliferation and differentiation. By using the combined techniques of patch clamp, digital imaging fluorescence microscopy, and molecular biology, we are currently studying the roles of ion channels and intracellular  $Ca^{2+}$  in regulating vasomotor tone, and pulmonary vascular smooth muscle proliferation and apoptosis. Furthermore, whether and how dysfunctional voltage-gated  $K^+$  (Kv) channels and upregulated transient receptor potential (TRP) channels in pulmonary arterial smooth muscle cells (PASMC) contributes to the development of pulmonary hypertension is also being investigated. The aims of the ongoing research work in the laboratory are: 1) understand the cellular and molecular mechanisms involved in hypoxia-mediated inhibition of Kv channels in PASMC, 2) investigate the molecular mechanisms of PASMC proliferation and apoptosis, 3) specify the pathogenic roles of  $K^+$  (e.g., Kv) and  $Ca^{2+}$  (e.g., TRP) channels in pulmonary arterial hypertension, 3) search for new therapeutic approaches for pulmonary hypertension (e.g.,  $K^+$  channel openers, pro-apoptotic/anti-proliferative agents), 4) determine the genetic variances associated with the susceptibility to develop idiopathic and thromboembolic pulmonary hypertension, and 5) identify the mechanisms that regulate membrane trafficking of ion channels in pathogenesis.

**You-Yang Zhao, Ph.D. (Shanghai Institute of Biochemistry, Chinese Academy of Sciences)  
Assistant Professor**

Recovery of endothelial integrity after vascular injury is vital for endothelial barrier function and vascular homeostasis. Endothelial dysfunction plays a critical role in the initiation and progression of vascular diseases such as acute lung injury/acute respiratory distress syndrome, and atherosclerosis. A part of the research in the lab is to elucidate the molecular mechanisms of endothelial repair following inflammatory lung vascular injury, understand the mechanisms of action of stem/endothelial progenitor cells-mediated endothelial regeneration, vascular repair, and neovascularization using the unique mouse model with endothelial cell-restricted deletion of FoxM1 (JCI, 2006, 116, 2333-43; JEM, 2010, 207:1675-85), and other genetically modified animal models.

Pulmonary hypertension is a progressive disease with poor prognosis and high mortality. We are currently investigating the underlying molecular basis using genetically modified mouse models, pharmacological approaches, and patient samples. It is our hope to provide novel therapeutic approaches for the prevention and treatment of this devastating disease with the integrated and translational approaches. We have demonstrated a critical role of Caveolin-1, the scaffolding protein of caveolae in the pathogenesis of pulmonary hypertension and identified a novel mechanism of pulmonary hypertension in mice and humans through PKG tyrosine nitration-mediated impairment of PKG activity (JCI, 2009, 119, 2009-18).

## GRADUATE STUDIES

### Overview

The doctoral program in pharmacology is designed as a five to six year curriculum starting in the fall semester. Successful completion of the program requires the student to fulfill the formal course requirements, pass the Graduate College Preliminary Examination, and successfully defend the thesis based on original laboratory research.

Students, throughout their residency, will be required to participate in the departmental seminar series and student Research Forum (PCOL 595) held regularly during the fall and spring semesters. Students are also expected to attend the weekly Research Forum and special seminars by visiting professors sponsored by the department. Speakers will be available for informal meetings with interested students to discuss their own research problems as well as to advise students on career opportunities and on postdoctoral training at their home institutions.

### Formal Course Work Requirements

The Graduate College sets minimum Ph.D. degree requirements, (96 semester hours, of which 20 must be in formal courses), but allows each department to set its specific requirements. The Department of Pharmacology requires all students to have a rounded knowledge of biochemistry and molecular biology, cell physiology, and pharmacology. The formal course work requirements are outlined as follows:

### FIRST YEAR PHARMACOLOGY COURSES

#### Graduate Education in Medical Sciences (GEMS) Core Courses

#### *Fall*

##### *Core courses (3 required)*

GLCS 500 Physiology	TTh 9:00 AM-10:25 AM 1020 COMRB	3 hrs
GCLS 501 Biochemistry	MWF 8:30-9:20 1017 MBRB (auditorium)	3 hrs
GCLS 502 Molecular Biology	TTh 10:30-12:00 1020 COMRB	3 hrs
GCLS 503 Cell Biology	MWF 9:30-10:20 1017 MBRB	3 hrs

##### Required courses

GCLS 504 Research Methods I	TTh 1:30-4:00 1017 MBRB	1-2 variable hrs
GCLS 506 GEMS Research Rotation	arranged	2 h

#### *Spring*

GCLS 505 Research Meth. II	TTh 1:30-4:00 small group rooms	1-2 variable hrs*
GCLS 515 Receptor Pharmacology & Cell Signaling	MW 2:30-4:00 4175 COMRB	3hr
PCOL 501 Medical Pharmacology I	ARRANGED 221 CMW	3hrs

GCLS 506 GEMS Research Rotation            arranged                            5 hrs

If a student already has taken extensive coursework in Pharmacology, one of the following courses may be substituted, after consultation with the Director of Graduate Studies:

GCLS 510 Integrative Biology            MW 10:00-11:30            1017 MBRB            3 hrs

GCLS 511 Molecular Genetics            TTh 9:30-11:00            1017 MBRB            3 hrs

BCMG 513 Structure of Biopolymers, MWF 9:00    1009 MBRB            3 hrs

PHYB 552 Translational and Applied Physiology -                            3 hrs

## **SECOND YEAR PHARMACOLOGY COURSES**

### **Fall**

Medical Pharmacology II PCOL 502, 3 credits

Scientific Integrity and Responsible Research (GC 401), 0 credits

Pharmacology Seminar (PCOL 595), 1 credit

Ph.D. Thesis Research (PCOL 599), 8 credits

\*GC 470 - Essentials for Animal Research. 1 credits (\*only required for students whose research involves the use of animals).

### **Spring**

Pharmacology Seminar (PCOL 595), 1 credit

Ph.D. Thesis Research (PCOL 599), 1-16 credits

Pharmacology Elective (2 credits)

## **Pharmacology Electives**

All students must take one Pharmacology elective. Individual faculty members in the department may require their students to take additional course work. The Department of Pharmacology currently offers three courses on advanced topics. These courses are all for 2 credits. Two courses will be presented each spring quarter; each course will be presented on alternate years. (*A student may be allowed to take a desired Pharmacology elective in their 1<sup>st</sup> year if it won't be given in their second year. This requires prior approval by the Director of Graduate Studies*). The courses are as follows:

PCOL 510 Molecular Pharmacology of Platelets, Thrombosis and Vascular System

PCOL 530 Pharmacology and Biology of the Vessel Wall

PCOL 540 Ion Channels: Structure, Function, Pharmacology and Pathology

PCOL 550 Biology and Pharmacology of the Lung is a required course for trainees in the Lung Biology and Pathobiology Training Program. It will not count towards the

Pharmacology elective requirement.

### **THIRD AND SUBSEQUENT YEARS**

Students must register for PCOL 595 (1 credit) and PCOL 599 (variable credit, 1-16) each fall and spring semester, and for PCOL 599 in summer to extend their stipends from an assistantship or fellowship. Full-time status is considered 12 hours in regular semesters, 6 in summer. PCOL 595 and 599 grades are either S (satisfactory) or U (unsatisfactory). In accordance with Graduate College policy, “an unsatisfactory grade can be assigned at any time when the student is not making satisfactory progress in thesis research. If this should occur, the status of the student will be reviewed by the advisor, the director of graduate studies, and the Graduate College, and the student may be dismissed from the Graduate College.”<sup>1</sup>

### **REQUIREMENTS FOR MD/PHD STUDENTS**

For MD/PhD students, the Medical School basic science curriculum fulfills most of the core GEMS course requirements. In addition, students have already completed rotations and start on their thesis research upon entering the PhD phase of their training. As such, they are functionally classified as second year PhD students and will fulfill the corresponding requirements as described in detail above and as outlined below.

#### **Coursework Requirements**

##### Fall semester:

GC 401 Scientific integrity and responsible research (0 credits)  
\*Methods I GCLS 504 (1- 2 credits)

\*A total of 3 credits from Methods I and II combined are required

##### Spring Semester

\*Methods II (GCLS 505) (1- 2 credits)  
Receptor Pharmacology & Cell Signaling (GCLS 515) 3 credits  
Advanced Pharmacology Elective course (2 credits):  
Choose from: Ion Channels, Platelet course or Vascular Biology course (see above)

#### **Research Committee**

MD/PhD students will establish their Research Committee in the Spring semester of their first year in the PhD program (see below for details).

#### **Research Forum**

MD/PhD students will present a talk in the Research Forum in the Spring semester of their first year in the PhD program (see below for details).

#### **Graduate College Preliminary Exam**

MD/PhD students are required to take their Preliminary Exam by August 15 of their first year in the PhD program (see below for details).

### **GENERAL INFORMATION AND POLICIES**

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<sup>1</sup> See “Grades”, <http://grad.uic.edu/cms/?pid=1000041>.

## Academic Standards and Probation

Students are required to take a full course load their 1<sup>st</sup> semester and are not allowed to drop a course part way through the semester nor take an "Incomplete" to avoid a bad grade and/or probation. Exceptions to this policy will only be considered for extenuating circumstances (e.g., emergency family situation; severe health problems) and will require consultation with and approval by the Graduate Committee prior to initiating any changes in coursework.

The Graduate College requires graduate students to maintain a GPA of 3.0 (out of 4.0) to remain in good academic standing. Although Graduate College policy is to allow students whose GPA falls below 3.0 up to two semesters on probation to bring their GPA up to 3.0, departments are given the authority to impose stricter standards and place additional limits on probation, provided students are notified in writing. In keeping with this policy, the Department of Pharmacology has set more rigorous standards for academic performance that *supersede* the Graduate College guidelines as follows.

**Students who get a grade of C for 6 credits or more of course work (e.g., C's in two 3 credit courses) or get a "D" or "F" in any course will be dropped from the program. Students with a GPA below 3.0 after the 1<sup>st</sup> semester are required to make up the deficit and be in good academic standing (3.0 GPA) by the end of Spring semester of their 1st year.**

*Petitioning the Graduate Committee:* If a student has 3 or less deficit grade points (i.e., credits of "A" needed to bring the GPA to 3.0) remaining by the end of the Spring semester of their first year they may petition the Graduate Committee to remain in the program. If agreed to by the Graduate Committee, a student will be allowed to continue as a graduate student, but stipend support is not guaranteed. Students remaining in the program under these conditions must have a 3.0 GPA by the end of the Fall semester of their second year. Students who do not meet these standards will be dismissed from the program with no further opportunity for appeal.

## Advisors

Dr. Thomas Guenther will function as advisor to new students until they have completed arrangements for a thesis advisor. Dr. Randal Skidgel is also available to advise students during their first year. The faculty and students in the department work together in guiding beginning graduate students into a new professional environment during the predoctoral training program. Students should always feel free to consult with their thesis advisors, other faculty members, or Dr. Malik.

## Lab rotations: Affiliation with thesis advisor

Incoming students "rotate" through a minimum of three laboratories during their first year. These rotations are arranged by Dr. Guenther and last approximately 8-10 weeks. A mini-seminar will be arranged before rotations begin at which faculty who are participating in rotations will give brief summaries of their research to the incoming students. Students will then be asked to choose 3 potential faculty members for their first 2 rotations. To allow greater flexibility, the third rotation will be chosen by the student near the end of completion of the second rotation period. *Students who wish to rotate in a laboratory outside the department must first talk with Dr. Guenther, who will then contact the Director of Graduate Studies from the other department for their approval.*

The purpose of these rotations is to provide the student with a working knowledge of basic laboratory techniques and, more importantly, to provide the student with the information necessary to make a rational choice of thesis advisor. Students who have defined interests before starting the program may petition to truncate this process. All students are expected to affiliate with a major advisor at the end of this period (usually April-May). Permanent laboratory assignments must be approved by Dr. Malik in consultation with Dr. Guenther and the graduate committee. Each student must fill out a "Nomination of Thesis Advisor" form.

## **Research Forums**

Students in their second year and beyond will present their research once during the academic year during the weekly student research forums. Students will provide their titles one month in advance of their scheduled presentation. It is the responsibility of the student's lab mates to set up before and clean up after the presentation.

## **Establishment of Departmental Research Committee**

Each student has a departmental research committee which oversees the student's research throughout the student's tenure in the program. This committee is composed of the student's advisor and two other members of the campus faculty. This committee is chosen for its expertise and is not limited to members of the Department of Pharmacology. The composition of the committee must be submitted to Dr. Skidgel for approval. It is expected that the research committee will be established by the spring semester of the second year at which time the student will meet with the committee to outline and discuss a preliminary thesis proposal. This committee will meet each semester (Fall and Spring) thereafter to monitor the student's progress. The outcome of the research committee meeting will determine the PCOL 599 grade. The student will use this meeting each semester to present a thesis proposal to the committee as soon as the proposed thesis work is clearly defined. It is expected that this committee will become the core members of the Graduate College Preliminary Exam Committee and the Thesis Committee.

## **Graduate College Preliminary Examination**

Students are required to successfully pass the Graduate College Preliminary Examination prior to the end of their second year in the program (August 15). It is not necessary to have completed all of the didactic coursework before taking the preliminary examination. A minimum of 1 year must elapse after passing the Preliminary Examination before the defense of the Thesis Dissertation. Please refer to the Graduate Catalog for Graduate College policies regarding this examination.

The format for this examination is established by each department. The examination in Pharmacology is composed of a Research Proposal prepared in the form of an NIH Postdoctoral Fellowship (without budget and other ancillary pages) which is then defended in an oral examination. The proposal may be on any appropriate research topic including the area in which the student will work for his/her dissertation. It need not be based on any preliminary data obtained by the student. Specific instructions are contained in the departmental Preliminary Examination packet.

In consultation with your advisor, select a Preliminary Examination Committee. The chair of the Committee must be a full member of the UIC Graduate Faculty. The PI serves as a member of the committee, but shall not function as chair of the committee. The Chair of the committee must be a tenured faculty member who will be responsible for enforcing the rules of the Prelim Exam. Research Faculty from the PI's laboratory will not be allowed to serve on the committee.

## **Thesis Committee and Defense**

### *Pre-defense Thesis Committee Meeting*

Please contact Cynthia Sanders to obtain a "Pre-defense Thesis packet" that will contain the required forms for the pre-defense committee meeting and helpful information regarding producing high resolution figures for the thesis, how to use and properly cite material that is already published, etc.

The departmental requires that students have a meeting with their thesis committee after completing all coursework and most of the experimental work for the dissertation. This should occur approximately 4-6 months before completing the thesis and defense. This will require that the student submit the

committee recommendation form to the graduate college at least 3 weeks prior to the desired meeting time for approval as the meeting cannot take place until the committee has been approved by the Graduate College. Note that the Graduate College requires one member to hold an appointment outside of the Department of Pharmacology. The student will present an overview of their results to the committee, which will then decide whether the student is ready to proceed to write the thesis.

### *Intent to Graduate*

During completion of the thesis, students declare their intention to graduate on the Intent to Graduate online form (Pending Degree List). The form must be submitted to the Graduate College before the semester deadline for the term in which the student wants to graduate. This date can be found in the academic calendar and is usually about three weeks after the start of the term. Access the PDL form on UIC Web for Student. For more information on graduation, visit:

<http://grad.uic.edu/cms/?pid=1000030>

### *Dissertation & Defense*

The doctoral thesis is a permanent record of the scholarly work performed as a requirement for the PhD degree. Its quality is a reflection on the department, student and advisor. The thesis advisor bears the primary responsibility for assuring that the highest level of quality is met as stated in the official UIC Graduate College Thesis Manual:

“The Graduate College ... has delegated the responsibility for quality control of content, most aspects of format, choice of style, proofreading, grammar (including word divisions and abbreviations), underlining, references and citations, etc., to the graduate program. Unless a program has provided an alternative mechanism, **the primary responsibility for this review must be assumed by the advisor. The thesis advisor is the closest representative of the Graduate College to the student. S/He is the best person to function as the primary editor.**” It is the student’s responsibility to complete the initial draft early enough to allow the advisor sufficient time to edit the thesis and assure that the final product is acceptable before submission to the thesis committee, **which should occur at least 3 weeks before the defense.** To guarantee that this is carried out, the advisor must sign the **Thesis Date Approval Form**, which the student will submit to Cynthia Sanders before setting an official thesis defense date. After Approval, see Laura Foote to reserve a seminar room for your dissertation defense. The Graduate College requires that the defense be publicly announced at least one week prior to its occurrence.

By signing the statement, the thesis advisor certifies that the thesis is a final draft, comparable in form to a work that would be submitted to a journal or publisher for publication. A work in rough draft form will not be acceptable, and should not be certified as acceptable by the thesis advisor. The student and thesis advisor should not expect that thesis committee members will provide extensive editorial improvements. The thesis committee’s responsibility is to judge the overall scientific quality, content, whether the conclusions are supported by the data, etc. Should the committee decide that the written thesis is not of an acceptable quality for their review, they can ask for a delay of the defense until this is rectified.

After a successful oral defense and correction of the thesis, according to suggestions by the committee, the final version of the thesis must be approved by the thesis committee. Students must then submit a final copy to the Director of Graduate Studies (Dr. Randal Skidgel) for departmental approval before submission to the Graduate College for their approval. Student deadlines (postdoctoral or job start dates, Medical School graduation for MD/PhDs, etc.) will not be accepted as excuses for skipping these important steps. Students must plan ahead far enough to assure that these do not become issues. Students then must submit two copies of their defended and departmentally approved dissertation to the Graduate College by the deadline for that term (listed in the academic calendar; usually about 6 weeks before the end of the semester). If the thesis is submitted after the deadline, the student will officially graduate the following semester, although the student is not required to register for the

following semester. Detailed guidelines for preparation of the written thesis can be found in the UIC Graduate College Thesis Manual online at: <http://grad.uic.edu/pdfs/thesismanual.pdf>.

The deadlines, Thesis Manual, graduation request forms, and dissertation committee forms will be found on the Web site of the Graduate College at: <http://grad.uic.edu/cms/?pid=1000027>. Cynthia Sanders will help you in checking the format and adhering to the guidelines. Electronic submission of the thesis became mandatory effective Fall 2011. Please see <http://grad.uic.edu/cms/?pid=1000916>.

Once your thesis format is approved by the Graduate College the student is responsible for providing a PDF copy of the entire thesis, identical to that submitted to and approved by the Graduate College to the Department. The Department gives a copy of the bound thesis to the student and his or her advisor. The last copy will be donated to the departmental library (Room 419 CMW).

### **Expectation of Publication**

The Department of Pharmacology expects that each student will have at least one first author paper published or accepted for publication before completing his or her PhD. This is an important part of graduate education and is very valuable to the student who will be looking for postdoctoral positions or other job opportunities after graduation.

### **Academic Integrity**

Students are expected to conduct themselves in a manner in accordance with the university standards of academic honesty and integrity. To view the graduate college's policy on academic integrity, visit <http://grad.uic.edu/cms/?pid=1000031>. The Graduate College course, "Scientific Integrity and Responsible Research" is required for all students and provides an introduction to some of the issues, but is not exhaustive. Students are responsible for their own actions and if there is ever any question, you should consult with your advisor or other faculty members in the department for their advice. Students found to be in violation of University standards of academic integrity may be subject to discipline under the Student Disciplinary Procedure. More information as to what constitutes just cause for discipline and related topics can be found at:

<http://www.uic.edu/depts/dos/docs/StudentDisciplinaryPolicy0809withpagenumbersandcov.pdf>

### **Plagiarism**

Plagiarism (i.e., representing others' work as your own) is an important and sometimes misunderstood concept that is relevant to papers written for coursework, scientific writing, grant proposals, and the PhD thesis. It is never acceptable. This includes, but is not limited to using statements (except when extensively modified) from review articles, internet sites and other published works, introductory material for papers, and grants. To give students a clearer understanding of what plagiarism is, so it can be avoided, the following excerpt is provided from *A Pocket Guide to Writing in History*, 4th edition written by Mary Lynn Rampolla and published by Bedford / St. Martin's [bedfordstmartins.com](http://bedfordstmartins.com) (New York – Boston, 2004) pp. 70- 72:

Plagiarism is the act of taking the words, ideas, or research of another person and putting them forward without citation as if they were your own. It is intellectual theft and a clear violation of the code of ethics and behavior that most academic institutions have established to regulate the scholastic conduct of their members. Colleges and universities have their own policies that define plagiarism and establish guidelines for dealing with plagiarism cases and punishing offenders, but the penalties for plagiarism are usually severe, ranging from an automatic F in the course to temporary suspension or even permanent expulsion from the school. Plagiarism, in short, is considered a very serious academic offense. If we look simply at the dictionary definition, it would seem that acts of plagiarism are readily identifiable. And, indeed, some instances of plagiarism

are obvious; deliberately copying lengthy passages from a book or journal article, or purchasing or downloading whole papers and submitting them as your own work, are clear-cut examples of plagiarism. However, although some students unfortunately make a conscious decision to plagiarize, many more do so inadvertently. This is because unlike the instances cited above, some situations in which you might use the words or ideas of another may seem murkier. Because of its seriousness, it is essential that you know exactly what kinds of acts constitute plagiarism. This chapter will clarify the concept and give you some advice on how to avoid unintentional plagiarism.

6a. What is plagiarism?

Read the following scenarios. Which of these would be considered plagiarism?

- A student borrows a friend's essay to get some ideas for his own paper. With his friend's permission, he copies portions of it, taking care, however, to cite all the sources his friend included in the original.
- A student finds useful information on a Web site that is not under copyright. She downloads and incorporates sections of this Web site into her paper, but does not cite it since it is in the public domain.
- A student derives some key ideas for his paper from a book. Since he doesn't quote anything directly from this book, he doesn't provide any footnotes. He does, however, include the book in his bibliography.
- A student modifies the original text by changing some words, leaving out an example, and rearranging the order of the material. Since she is not using the exact words of the original, she does not include a footnote.

The answer is that *all four* of these scenarios illustrate examples of plagiarism. In the first instance, the issue is not whether the student has permission from his friend to use his or her work. As long as the student is submitting work done by another as his own, it is plagiarism. Citing the sources that his friend has used does not mitigate the charge of plagiarism. In the second example, the fact that the student has used material that is not protected by copyright is irrelevant. She is guilty of plagiarism because she has submitted the words of another as her own. The third instance illustrates that definition of plagiarism encompasses not only the use of someone else's words, but also of their ideas; you must *always* acknowledge the source of your ideas in a footnote or endnote, even if you specifically include the text in your bibliography. Finally, in the fourth example, changing some of the words, reorganizing the material, or leaving out some phrases does not constitute a genuine paraphrase; moreover, even an effective paraphrase requires a footnote.

### **Attendance at Departmental Seminars and Special Lectures**

All students are required to attend departmental seminars, research forums, and special lectures unless there is a conflict with scheduled course work. If unable to attend a seminar, the student should leave her or his name and the reason for absence with Cynthia Sanders. **If a student misses more than three departmental seminars or three research forums without a valid excuse, a grade of U (unsatisfactory) in PCOL 595 will be recorded for that term.** Proof of attendance is required to receive credit. There will be a sign in sheet for research forums and departmental seminars.

### **Vacation**

Based on University policy, students supported on assistantships or fellowships are permitted to take not more than 2 weeks (10 working days) vacation during one calendar year. This includes time taken off during semester breaks, etc, but is in addition to official university holidays (e.g. Independence Day, Memorial Day, Thanksgiving, etc.) All vacations must be approved by the major advisor, and should also be reported to the departmental office well in advance of the date of leaving.

### **Postgraduate Placement Ads**

The department maintains a job opportunity bulletin board on the west wall of the main corridor leading to the entrance of the departmental office. This board contains current job advertisements received by the departmental office and by individual faculty members. In addition, fellowship announcements as well as announcements for opportunities for research funding are also posted on the same bulletin board on the west wall. Before seeking a postdoctoral fellowship or other position, which is the responsibility of the student, you are urged to consult with your thesis advisor and other faculty.

### **Disposition of Laboratory Notebooks**

All laboratory workers keep chronological laboratory notebooks of their experiments. **In all cases these notebooks and related data (electronic files, CDs, etc.) are the property of the laboratory rather than the person keeping the records.** Where appropriate, copies of the notebook can be made for the record keeper or other laboratory personnel.

### **Training Grants**

Qualified United States citizens and permanent residents are eligible for positions on one of several training grants in the College of Medicine. In these NIH funded grants, students draw on the knowledge of faculty members across multiple disciplines and numerous departments at the University of Illinois at Chicago. Each training grant generally has more than 30 independent investigators with strong research and training backgrounds. Students interested in obtaining a position on one of the training grants may be asked to submit an application. Trainees will take courses and participate in symposiums and special seminars.

#### *Lung Biology and Pathobiology Training Program*

This NIH-sponsored institutional training program was born out of our commitment to providing a research training opportunity that emphasizes comprehensive research in biology and pathobiology of lungs. Our goal is to provide state-of-the-art research training for a select group of predoctoral and postdoctoral trainees who aspire to research careers. The program emphasizes integrative and systems biology. Three general areas have been incorporated into the overall theme of the program: (1) Vascular Biology and Lung Injury and Repair, (2) Cellular and Humoral Basis of Lung Injury, and (3) Cell Signaling and Regulation of Lung Function in Health and Disease. The training program emphasizes the interdisciplinary nature of contemporary research in areas relevant to lung biology and pathobiology in an environment that fosters independent and creative thinking with the objective of training future research leaders.

For more information, please visit: <http://www.uic.edu/depts/mcph/training.htm>

### **Student Awards**

The department gives three student cash awards that are announced at the awards banquet during the annual Pharmacology retreat.

*Klaus Unna Award:* This award is based on scientific excellence, achievement and contributions to the department during the student's tenure, as evidenced by: high quality publications, awards/honors, fellowships and, service to the department. As such, it usually is given to a more "senior" student.

Eligibility: Any current student or students who will officially graduate no earlier than the Fall Semester (i.e., students who defended their thesis this summer, but did not meet the deadline for submission of the final thesis to the Graduate College are still eligible)

Nomination:

- 1) A letter of nomination from the advisor detailing why the student is deserving of the award.
- 2) A copy of the student's CV.
- 3) A letter from the student outlining their accomplishments while a student in our program.

### Previous Klaus Unna Award Winners

1985 Robert M. Claudle  
1986 Joanne M. Hettasch  
1990 Andre Terzic  
1992 Lynn Fitzgerald and Tomislav Dragovic  
1993 Irina Knezevic and Bratislav Velimirovic  
1994 Catherine Borg and Gang Luo  
1996 Marta Margeta and Gerd McGwire  
1997 Tina Taylor  
1998 Yasmine Djellas and Abla Albsoul  
1999 Duscia Bajic  
2000 Claudie Hecquet  
2001 Raudel Sandoval  
2002 Richard Bodnar  
2003 Joseph Schober and Caroline Marty  
2004 Jasna Ajdic  
2005 Jasmina Profirovic  
2006 Mike Broman  
2007 Shafi Kuchay  
2008 Peter Flevaris  
2009 Subhashini Srinivasan  
2010 Erica Southgate

### *The Albert and Doris Woeltjen Student Achievement Award*

This award will be given on an annual basis to the student who has achieved the most in the area of research in the last academic year. This award is focused on research accomplishments as evidenced by outside awards, travel awards, invited presentations at national or international meetings, publications, pre-doc fellowships, etc. The awards, etc. must have been given within the past academic year and only papers published (hard copy or online) or in press in that time frame will be considered.

Eligibility: Any current student or students who will officially graduate no earlier than the Fall Semester (i.e., students who defended their thesis this summer, but did not meet the deadline for submission of the final thesis to the Graduate College are still eligible)

#### Application Requirements:

1. A letter of nomination from the advisor detailing why the student is deserving of the award.
2. A page listing the research accomplishments of the student in the last year (Awards, publications, invited presentations, etc.)
3. Relevant publications or other supporting material related to the student's research accomplishments

### Previous Albert and Doris Woeltjen Student Achievement Award Winners

2003 Michael Holinstat  
2004 Douglas Yau  
2005 Masakatsu Nanamori  
2006 Fadi Khasawneh  
2007 Jia Chen  
2008 Hong Yin  
2009 Brendan Quinn  
2010 Frank Kuhr

### *The Albert and Doris Woeltjen Best Poster Awards*

Awards will be given to the top 3 posters presented by students at the annual Pharmacology Retreat.

Eligibility: Only current students who submit an abstract and attend and present a poster at the Annual Retreat will be eligible to compete.

### Previous Albert and Doris Woeltjen Best Poster Awards Winners

2004	1 <sup>st</sup>	Matvey Gorovoy
	2 <sup>nd</sup>	Fadi Khasawneh
	3 <sup>rd</sup>	(tie) Jasna Ajdic Marjanovic
	3 <sup>rd</sup>	(tie) Douglas Yau
2005	1 <sup>st</sup>	Fadi Khasawneh
	2 <sup>nd</sup>	(tie) Matvey Gorovoy
	2 <sup>nd</sup>	(tie) Masakatsu Nanamori
	2 <sup>nd</sup>	(tie) Douglas Yau
2006	1 <sup>st</sup>	Shafi Kuchay
	2 <sup>nd</sup>	Nicole Hajicek
	3 <sup>rd</sup>	Jia Chen
2007	1 <sup>st</sup>	Panagiotis (Peter) Flevaris
	2 <sup>nd</sup>	Frank Kuhr
	3 <sup>rd</sup>	Kelly Barrett
2008	1 <sup>st</sup>	Frank Kuhr
	2 <sup>nd</sup>	Subhashini Srinivasan
	3 <sup>rd</sup>	Aaron Place
2009	1 <sup>st</sup>	Nicole Hajicek
	2 <sup>nd</sup>	Katy Wong
	3 <sup>rd</sup>	Kamran Mirza
2010	1 <sup>st</sup>	Jessica Lowry
	2 <sup>nd</sup>	Katy Wong
	3 <sup>rd</sup>	Emily Vandenbroucke

### **Graduate Student Travel**

Student travel funds to scientific meetings are at a premium. The department has no funds designated for student travel. Both the Graduate College and Graduate Student Council have limited funds for students making presentations, which are made available upon application for specific meetings. Applications are available on line at <http://grad.uic.edu/cms/?pid=1000086> and should be completed according to the closest deadline following your travel. The Graduate College deadlines are September 30, January 31, and May 31,. The Graduate Student Council deadline is the 15th of the month prior to travel. Students cannot assume that the submission of an abstract for a meeting will guarantee funding nor should any student automatically expect full reimbursement for travel expenses. Funding from the advisor's grant is at his or her discretion.

## CURRENT GRADUATE TRAINING PROGRAM

2011

**Andrew Barazia**  
**Peter Hart**  
**Kevin Kruse**  
**Juyoung Kim**  
**Tina Perkins**  
**Venkateswaran Ramamoorthi Elangovan (J. Garcia)**  
**Dheeraj Soni (C. Tirupathi)**

2010

**Ruby Ferndandez**  
**Melissa Geyer**  
**Jessica Wilson (MD/PhD, J. O'Bryan)**

2009

**Brian Burmeister (G. Carnegie)**

The adult heart responds to injury or stress by activating a variety of intracellular signaling pathways that promote re-expression of an embryonic gene program, myocyte hypertrophy, and remodeling of the extracellular matrix. Collectively, these changes, defined as pathological cardiac remodeling, are associated with the progression of dilated cardiomyopathy and congestive heart failure. Growing evidence has implicated oxidative stress as a key factor in these maladaptive processes, however the precise signaling mechanisms involved are not well understood.

I am currently investigating the regulation of protein kinase D (PKD) in response to oxidative stress. We have previously demonstrated that the scaffold protein AKAP-Lbc facilitates PKD activation, leading to the de-repression of MEF2 transcription and the induction of hypertrophic cardiac gene reprogramming events. Recently, we identified the protein tyrosine phosphatase Shp2 as a component of the AKAP-Lbc signaling complex. Our preliminary data indicates that Shp2 may negatively regulate PKD activity in response to oxidative stress.

I am currently testing the hypothesis that AKAP-Lbc functions as a scaffold for PKD and Shp2, forming a signaling complex that regulates oxidative stress-induced activation of PKD and thus cardiac hypertrophy and remodeling. Under normal conditions Shp2 may act to inhibit PKD activity that is basally stimulated by Src family protein tyrosine kinases. Under pathological conditions of oxidative stress however, PKD will become preferentially activated due to oxidation of the Shp2 catalytic site and inhibition of Shp2.

**Nazila Daneshjou (A. Malik/Y. Komarova)**

The endothelium lining the blood vessel wall forms a semi-permeable barrier that separates plasma proteins and cells from underlying tissue. Dysfunction of endothelial barrier leads to permeability increase accompanied by protein-rich edema as well as infiltration of blood cells into the interstitial space. The monomeric RhoA-GTPases Rac1, Cdc42, and RhoA play a critical role in regulating endothelial barrier function. Stable Vascular Endothelium (VE)-cadherin homophilic interaction, the main adhesive complex of adherens junction (AJ), causes an increase in the activity of Rac1 and Cdc42, whereas activation of RhoA leads to destabilization of AJs. The purpose of my study is to determine the causal relationship between Rac1 activity at AJs and stability of VE-cadherin mediated

adhesion. I have utilized a photo-activatable Rac1 probe (mCherry-PA-Rac1), consisting of a constitutively active Rac1 (V12) mutant fused to a photo-activatable LOV (Light Oxygen Voltage) domain of phototropin1 from *Avena Sativa*, as a tool to activate Rac1 locally. I demonstrated that photo-activation of PA-Rac1, but not a light insensitive probe bearing a mutation in the LOV domain (PA-Rac1-C450A), induced VE-cadherin clustering with a rate constant of  $0.363 \pm 0.223 \text{ min}^{-1}$  in human dermal microvascular endothelial cells. Interestingly, photo-activation of PA-Rac1 also resulted in junctional accumulation of IQGAP1, a scaffold protein that sequesters GTP-Rac1 and prevents GTP hydrolysis, suggesting that these two events might occur in concert. Furthermore, down regulation of IQGAP1 using the siRNA technique completely inhibited clustering of VE-cadherin upon PA-Rac1 photo-activation. These findings suggest that clustering of VE-cadherin at AJs requires spatial activity of Rac1 and that Rac1 regulates the integrity of VE-cadherin adhesion in an IQGAP1-dependent manner.

### **Brian Estevez (X. Du)**

Platelets are anucleate blood cells which play fundamental roles in hemostasis and contribute to pathological thrombus formation. When blood vessels are damaged the underlying subendothelial matrix adhesive proteins are exposed causing platelet adhesion and eventually stable platelet thrombus formation. The platelet Glycoprotein receptor GPIb-IX-V (GPIb-IX) is important for the initial adhesion of platelets under the high shear flow conditions present in the arteries and capillaries. Under these conditions, the GPIb-IX complex mediates initial platelet adhesion and transmits intracellular signals promoting platelet shape change, granule secretion, thromboxane A<sub>2</sub> production, activating another platelet receptor integrin  $\alpha\text{IIb} \beta\text{3}$ . Full platelet response to the VWF:GPIb interaction requires TXA<sub>2</sub> synthesis and TXA<sub>2</sub> dependant granule secretion. However, the signaling mechanisms which regulate thromboxane production in platelets are poorly understood.

Lim kinase 1 (LIMK1) and Lim kinase 2 (LIMK2), form the Lim kinase family of serine/threonine kinases. In most cells, LIMKs mediate RhoGTPase induced cytoskeletal changes by enhancing the accumulation of filamentous actin (F-actin). LIMK1, but not LIMK2, has been shown to be expressed in human platelets. It is known that LIMK1 is phosphorylated and activated in platelets. However, the role of LIMK1 in platelet activation is unknown. Recently, our lab has identified a novel LIMK1-dependent GPIb-IX signaling pathway that stimulates TXA<sub>2</sub> synthesis and TXA<sub>2</sub>-dependent platelet activation. We have found LIMK1<sup>-/-</sup> platelets have a defect in GPIb-IX induced aggregation, secretion and TXA<sub>2</sub> production. However, the mechanism of action by which LIMK regulates thromboxane production is unclear. In addition, it is unknown whether LIMK1 plays a role in cytoskeletal reorganization in platelets. Understanding the signaling mechanisms which regulated thromboxane production will have therapeutic benefits as evidenced by the widespread usage of Aspirin as an anti-platelet agent.

### **Xiaowen Liu (J. Xu)**

Chemotaxis, or directed cell migration is essential for development, host defense and tumor invasion. Extensive studies have been conducted to understand the mechanisms for cell polarization and directional sensing. However, it is still a mystery as to how the chemotactic cells stop at correct destinations where they perform specific functions such as phagocytosis. MAPK kinases including ERK, JNK and p38 are involved in inflammation, apoptosis and migration. p38 MAPK has been shown to regulate neutrophil chemotaxis both *in vivo* and *in vitro*, though the underlying mechanisms remain unclear. We have found that p38 MAPK and ERK play opposite roles in terminating cell migration by using MAPK inhibitors and knock-down. My goal is to further investigate the mechanism of p38 MAPK and EKR in regulation of cell 'stop' signaling.

**Mary Maliakal (J. Yuan)****Maulik Patel (T. Kozasa)**

My lab is currently interested in the molecular mechanisms that regulate the activity of RH-RhoGEFs such as P115-RhoGEF, PDZ-RhoGEF, and LARG. RH-RhoGEFs are a subfamily of proteins, within the larger Dbl family of proteins, which are known to be specific GEFs for RhoA monomeric G-protein. RH-RhoGEFs help catalyze the exchange of GDP for GTP on RhoA thus initiating its downstream signaling events resulting in cellular proliferation, gene transcription, and cellular migration. What differentiates these RH-RhoGEFs from other members of Dbl family of proteins is the existence of the RH domain at its N-terminus. This RH domain interacts with  $\alpha$  subunit of the heterotrimeric G protein of the G $\alpha$ 12/13 family resulting in activation of their RhoGEF activity. Thus, RH-RhoGEFs provide a direct functional link from GPCRs coupled to G $\alpha$ 12/13 to RhoA signaling. Another mechanism by which the activity of these RH-RhoGEFs is regulated is via tyrosine phosphorylation. In fact, it has been reported that PDZ-RhoGEF is tyrosine phosphorylated downstream of GPCR activation by members of Focal Adhesion Kinase family, which consists of FAK and Pyk2. Tyrosine phosphorylation of PDZ-RhoGEF by FAK or Pyk2 is thought to result in positive regulation of its GEF activity. We are currently working on identification of the phosphorylated tyrosine residues of endogenous PDZ-RhoGEF from cancer cell lines. We aim to provide evidence through mutational analysis and biochemical techniques that phosphorylation of PDZ-RhoGEF indeed results in positive regulation of its GEF activity.

**Robert Tell (R. Benya)**

Gastrin Releasing Peptide is a peptide hormone which acts to regulate the normal gut function in humans. Its cognate receptor, GRPR, normally expresses in the stomach, pancreas, and brain. In many cases of colorectal cancer however, GRPR and GRP are aberrantly expressed by cancerous cells. Our work has shown that, contrary to many aberrantly expressed genes, GRPR has positive prognostic implications in patients whose tumors express the protein at a high level. Patients whose tumors highly express GRP/GRPR live 13.1 months longer on average compared to those who do not. Along with in vivo correlative studies, a number of phenotypic assays have shown that eliminating GRP signaling results in increased cellular invasiveness. This is thought of as an indicator of metastatic potential. Our current work focuses on the mechanism whereby GRPR might improve patient survival and decrease colorectal cancer cell invasiveness.

2008

**Farnaz Bahkshi (R. Minshall)**

Caveolin-1 (Cav-1) is required for caveolae formation but it also binds to signaling proteins such as endothelial nitric oxide synthase (eNOS), which generally negatively regulates their activity. Interestingly, activation of caveolae trafficking is associated with an increase in NO production. Here, we test the hypothesis that a NO feedback mechanism directly modifies the assembly and mobility of caveolae. We determined whether eNOS-derived NO affects Cav-1 oligomer stability by S-nitrosylation (SNO) of Cys156 and thereby regulates vesicular trafficking. Endothelial cells stimulated with TNF $\alpha$  or Ca $^{2+}$  ionophore A23187 for up to 4 hr were lysed and used to measure Cav-1 SNO by biotin-switch assay as well as Cav-1 oligomer stability in non-reduced SDS PAGE gels. TNF $\alpha$  and Ca $^{2+}$  increased NO production and Cav-1 SNO and also decreased Cav-1 oligomerization, which was blocked by L-NAME. We next transfected cells with GFP-tagged wild-type Cav-1 or Cys156Ser-Cav-1 mutant to determine the role of Cys156 in caveolin oligomerization, vesicle formation and trafficking as characterized by immunoblot analysis, TEM, and live-cell spinning disc confocal imaging. These studies revealed that Cys156Ser-Cav-1 mutant failed to form caveolae and that oligomers were less stable

compared to WT Cav-1. Cys156Ser-Cav-1 expressed in normal endothelial cells reduced caveolae trafficking velocity by 70% and decreased vesicle volume by 36%. Thus, S-nitrosylation of Cav-1 may be an important regulatory mechanism of caveolae formation and trafficking in endothelial cells.

### **Auditi DebRoy (C. Tiruppathi)**

Ca<sup>2+</sup> is an essential second messenger which controls a variety of crucial cellular functions. It regulates endothelial cell-cell and matrix tethering and actin-myosin contractile machinery, and therefore is important in the maintenance of vascular endothelial barrier. However, an increase in intracellular Ca<sup>2+</sup> concentration in endothelial cells leads to increased vascular permeability and tissue edema. The pro-coagulant protease thrombin mediates these effects by the activation of G-protein coupled Protease-activated Receptor-1 (PAR-1) expressed on the endothelial cell surface producing Inositol-1,4,5-trisphosphate (IP<sub>3</sub>)-mediated Ca<sup>2+</sup> store release from Endoplasmic Reticulum (ER) and Ca<sup>2+</sup> store depletion-mediated Ca<sup>2+</sup> entry (SOCE). The major Ca<sup>2+</sup> influx pathway is Store-operated Ca<sup>2+</sup> entry (SOCE) in vascular endothelial cells. A number of previously published studies have shown Transient Receptor Potential Canonical Family of Channels (TRPC) expressed on the plasma membrane of endothelial cells to be responsible for SOCE. Recently, a relatively new protein was identified in the ER, Stromal Interacting Molecule 1 (STIM1) which functions as a “sensor” of store Ca<sup>2+</sup> concentration in ER. Upon thrombin-induced store Ca<sup>2+</sup> depletion, STIM1 molecules oligomerise to form “puncta” which interact with the plasma membrane-localized TRPC channels to activate Ca<sup>2+</sup> entry. Thus, TRPC-STIM1 co-signaling is required for SOCE in endothelial cells.

Our preliminary data show that bacterial cell wall component lipopolysaccharide (LPS) induces the expression of TRPC1 (the dominant TRPC isoform expressed in human endothelial cells) and STIM1 in human lung microvessel endothelial cells (HLMVECs). Further we observed an LPS pretreatment augmented thrombin-induced increase in Ca<sup>2+</sup> entry and permeability response. Importantly, on STIM1 gene promoter analysis, we found consensus binding sites for the pro-inflammatory transcription factor, nuclear factor- $\kappa$ B (NF- $\kappa$ B). This raises the intriguing possibility that LPS induces STIM1 transcription signaling via NF- $\kappa$ B in lung microvessel endothelial cells and thereby augments Ca<sup>2+</sup> entry and permeability response. My goal is to characterize the transcriptional mechanism of STIM1 gene expression in endothelial cells under basal and experimental sepsis condition and its consequence on PAR-1 activation-mediated Ca<sup>2+</sup> entry and increased lung vascular permeability. These studies are expected to provide new insights into the understanding of mechanisms of lung vascular hyper-permeability associated with sepsis. I also want to determine the pathophysiological in vivo relevance of enhanced STIM1 expression. We measured lung capillary liquid permeability in wild-type (C57BL6J) mice. In LPS primed lungs, we observed augmented liquid permeability in response to PAR-1 peptide compared to control lungs indicating that LPS-induced STIM1 expression may contribute to hyper-permeability and pulmonary edema which is normally observed in septic shock.

The outcome of my studies will provide a comprehensive picture of the role of STIM1 signaling in the mechanism of lung vascular hyper-permeability associated with sepsis. Thus, an innovative and unique approach to eliminate vascular leak can be pursued by generating a very specific peptide drug to interrupt TRPC channel gating by STIM1 in endothelial cells.

### **Alexander Garcia (A. Malik)**

The endothelium is a monolayer of cells lining blood vessels forms a barrier that separates the circulating blood from the surrounding tissue. Endothelial adherens junctions (AJs) consisting of VE-cadherin and its associated catenins dynamically control the permeability of the endothelial barrier. IQGAP1 is a scaffold protein that associates with  $\beta$ -catenin and with the active (or GTP bound) forms of monomeric GTPase Cdc42 that plays an important role in improving the integrity of AJs. My research addresses the role of IQGAP1 interaction with AJs in regulating permeability of endothelial barrier. Lungs of IQGAP1<sup>-/-</sup> mice displayed a 2-fold greater lung capillary filtration coefficient (K<sub>fc</sub>) value, a measure of vessel permeability, after PAR-1 activation compared to WT. To address mechanism of IQGAP modulation of endothelial permeability, we next studied the PAR-1 response in lung microvascular endothelial cells. PAR-1 resulted in reversible association of IQGAP1 with AJs as

demonstrated by immunofluorescence and co-immunoprecipitation studies. The time course of IQGAP1 re-association with AJs correlated with activation of Cdc42 and AJ resealing, suggesting that IQGAP1 temporally and spatially coordinates Cdc42 activity and thereby the stabilization of AJs. Lung endothelial cells isolated from IQGAP1<sup>-/-</sup> mice demonstrated low basal activity of Cdc42 and impaired formation of AJs consistent with the role of IQGAP in regulating Cdc42 activity and thereby AJ integrity.

These data demonstrate the key role of IQGAP1 in the regulation of AJ integrity through its control of Cdc42 activity. The expression level of IQGAP1 may therefore be critical determinant of the magnitude of the increase in lung vascular permeability associated with acute lung injury.

### **Erin Kohler (K. Wary)**

Angiogenesis, the formation of neovessels from pre-formed blood vessels, occurs during development and plays an important role in diseases such as atherosclerosis, wound healing, and cancer. In vitro, transgenic, and knockout studies have provided evidence that vascular endothelial growth factor (VEGF) and its receptor (known as FLK1, VEGFR2, and KDR) play fundamental roles in the formation of blood vessels. FLK1 is one of the earliest and defining markers of endothelial cells (ECs). Inhibition of FLK1 signaling can impede wound healing and angiogenesis.

My research is to investigate the function of NANOG, a master transcription factor required for stem cell self-renewal, in ECs as they relate to angiogenesis and lung microvessel injury and repair mechanisms. We have observed expression of NANOG in ECs and a subset of tumor cell lines. NANOG and Fetal Liver Kinase (FLK1) expression in ECs are up-regulated following WNT3A stimulation. Chromatin immunoprecipitation (ChIP) and electrophoretic mobility shift assays (EMSA) revealed four NANOG binding sites in the FLK1-promoter sequence. NANOG depletion resulted in a decrease in FLK1 mediated EC proliferation in vitro and angiogenesis in vivo, seen using BrdU staining and Matrigel plug assays. Re-expression of FLK1 into NANOG knockdown HUVECs partially restored the proliferative and angiogenic defects in these cells. These unexpected results, therefore, support a potential role for NANOG in angiogenic and proliferative activities of ECs.

I will continue to extend upon these observations by testing the hypothesis that during angiogenesis or injury, endothelial cells express NANOG which induces dedifferentiation of a subset of cells into a "stem- or progenitor-like" state, by activating FLK1 and Cyclin D1 transcription or an OCT4/NANOG complex formation.

### **Myung-Jin Oh (I. Levitan)**

Oxidized low density lipoproteins (oxLDL) is an important factor in atherosclerosis. Our lab has shown that oxLDL can alter the biomechanics of endothelial cells, in particular the cell stiffness and contractility. It has been suggested that biomechanical changes can be a determinant for endothelial dysfunction and vascular remodeling. The underlying mechanism of how oxLDL induces cell stiffening is still poorly understood. Our goal therefore, is to understand the mechanism by which oxLDL induces cell stiffening and contractility in endothelial cells. The Rho-GTPases are a small family of proteins responsible for regulation of cellular functions such as the actin cytoskeleton, cell polarity, and microtubule dynamics. We believe the Rho-GTPases may mediate oxLDL induced cell stiffness and contractility and are currently testing the three most common Rho-GTPases: rhoA, rac1, and cdc42.

### **Bo Shen (X. Du)**

Integrins are adhesion receptors that connect cells to each other and to the surrounding extracellular matrix. Integrin beta1 was shown to play an important role in integrin outside-in signaling leading to cell spreading, retraction, and migration. Recently, our lab has found that the small G protein subunit Galpha13 directly binds to integrin beta3. After ligand binding to integrin alpha2bbeta3, Galpha13 binds to the beta3 cytoplasmic tail, activating Src, leading to RhoA inhibition and cell spreading. Meanwhile, direct binding of integrin beta1 cytoplasmic tail to purified Galpha13 was observed. However, the importance of this interaction is not clear, and little is known about the how Galpha13 mediates beta1-dependent integrin outside-in signaling. My recent work identified that Galpha13 mediates integrin beta1 outside-in signaling by binding directly to it, and identified the binding sequence of integrin beta1

to Galpha13. Integrin beta1 has been known to play a role in cancer metastasis, but the mechanism is very unclear. We have found that Galpha13 mediated integrin bata1 outside-in signaling regulates cell migration, and may play a key role in cancer metastasis. In summary, my overall goal is to elucidate the mechanism of Galpha13-mediated integrin beta1 signaling in the regulation of cell spreading and migration, and its potential function in the cancer metastasis.

### **Shalina Taylor (J. Xu)**

Our lab studies the role of neutrophils chemotaxis, which is important in physiological and pathological processes. Chemotaxis is the movement of a cell in response to a chemotactic gradient. Phagocytosis of the microorganism allows for the activation of NADPH oxidase and for degranulation. There are three types of granules found in neutrophils; azurophillic, specific, and your small granules. MPO is found in azurophillic granules, but the content in all granules contribute towards bacterial killing. Both NADPH and MPO are involved in the formation of reactive oxygen species. NADPH oxidase produces superoxide anions which is short lived and dismutates to hydrogen peroxide. In the presence of hydrogen peroxide and chloride MPO produces hypochlorous acid which is considered to be cytotoxic. My goal is to better characterize the role of myeloperoxidase during neutrophil chemotaxis. We plan to analyze the role of myeloperoxidase in mediating neutrophil chemotactic signaling pathways.

**2007**

### **Alejandra Chavez (D. Mehta)**

My research focuses on examining the role of the lipid enzyme Sphingosine Kinase 1 (SPHK1) in regulating angiogenesis. Our lab has shown that SPHK1 plays a key role in regulating the permeability of the endothelial barrier. Specifically, SPHK1, through the production of Sphingosine-1-Phosphate (S1P), is able to strengthen the endothelial junctions and hence mediates barrier strengthening after the barrier disruption that is caused by inflammatory stimuli, such as LPS or thrombin. I am interested in investigating how SPHK1 works in concert with Vascular Endothelial Growth Factor (VEGF), a permeability increasing agent and potent inducer of angiogenesis. VEGF promotes various cellular functions such as chemotaxis, proliferation, permeability and cell survival which have been shown to be important in eliciting a pro-angiogenic phenotype. SPHK1 induced S1P production has an opposing effect on intracellular permeability but is similarly involved in the stimulation of migration and cell survival. Because SPHK1 and VEGF have overlapping functions I am interested in the hypothesis that SPHK1 is important in VEGF angiogenic signaling. The goal of my research is to define the role of SPHK1 in orchestrating the complex signals that maintain the angiogenic program and barrier integrity.

### **Michael Keegan Delaney (X. Du)**

We are interested in the signaling mechanisms that regulate the procoagulant function of platelets. Agonist-induced platelet procoagulant activity is mediated by the externalization of phosphatidylserine (PS) and formation of platelet-derived microparticles (PDMPs). The exposure of PS by activated platelets is important for coagulation because PS functions as a catalytic surface for the  $Ca^{2+}$ -dependent assembly of serine proteases and their cofactors into enzymatic complexes that propagate the coagulation cascade, such as the tenase and prothrombinase complex. In addition, PDMPs also propagate the coagulation cascade because they express very high levels of externalized PS and are enriched in binding sites for coagulation factors. To date, the signaling mechanisms that regulate the externalization of PS and formation of PDMPs in platelets remains unknown. Using both a pharmacologic and genetic approach, we are currently identifying and characterizing the role of different proteins in regulating agonist-induced platelet procoagulant function. Delineating the signaling pathway that regulates microparticle formation and PS exposure in platelets has important therapeutic implications because these processes are important for hemostasis, thrombosis, and programmed cell death.

## **Adam Wieschhaus (A. Chishti)**

### **The Role of Dematin in Platelets**

Dematin is a peripheral membrane protein composed of two polypeptides of 48 and 52 kDa that assemble a trimeric complex. Each polypeptide is divided into two regions consisting of a unique N-terminal “core” domain and a C-terminal “headpiece” domain. Originally, dematin was isolated from the human erythrocyte membrane, but its expression has been found in many other tissues. In erythrocytes, dematin is a component of the junctional complex and links the actin-spectrin cytoskeleton to the plasma membrane. Dematin binds and bundles actin filaments in a phosphorylation-dependent manner. To determine the functional role of dematin, a dematin headpiece knockout (HPKO) mouse model was generated. The HPKO mice display mild hemolytic anemia, defects in erythrocyte shape and membrane stability, impaired wound healing, delayed cell migration, and enhanced fibroblast adhesion, consistent with dematin’s broad expression in cardiac, vascular endothelial, brain, skeletal muscle, and kidney tissues.

Our current studies are investigating the function of dematin in non-erythroid cells with a particular focus on platelets. The role of dematin in platelets may be significant because of the importance of the actin rearrangements in the regulation of platelet shape changes that are essential for the thrombotic cascade. Preliminary data indicate that dematin is expressed in platelets as a predominantly 52 kDa isoform. It is associated with the platelet membranes and binds to the scaffolding protein 14-3-3 $\zeta$ . Therefore, dematin may function at the platelet membrane as a molecular adaptor between the platelet receptors and the actin cytoskeleton via 14-3-3 $\zeta$ . The deletion of the mouse dematin headpiece domain *in vivo* causes defects in platelet spreading, aggregation, and secretion pathways. Based on these observations, we hypothesize that dematin plays a critical role in platelet physiology by participating in the reorganization of the actin cytoskeleton.

2006

## **Christina Chow (T. Kozasa)**

Many pathways of G $\alpha$ 13 signaling have been delineated, but the role of these pathways in human embryonic stem cells has not been widely studied. It has been shown that G $\alpha$ 13 is critical for embryonic development since G $\alpha$ 13 knockout mice die during embryonic development due to a deficiency in proper blood vessel formation and have fewer mature endothelial cells than wildtype mice. PAR-1 (the thrombin receptor) knockout mice have a similar phenotype to the G $\alpha$ 13 knockout mice, so we believe that together, these pathways are critical for angiogenesis and vascular remodeling during embryonic development. We are studying the role of G $\alpha$ 13 in the differentiation of human embryonic stem cells into mature endothelial cells, particularly downstream of thrombin/PAR-1 signaling. Additionally, we will study the role that two of the best-characterized effectors of G $\alpha$ 13, Rho-specific guanine nucleotide exchange factors (RhoGEFs) p115RhoGEF and LARG, play in this differentiation pathway.

## **Jessica L. Lowry (R. Skidgel)**

Acute inflammation is an important protective response to infections and harmful foreign substances. However, prolonged or chronic inflammation can lead to extensive tissue damage. During the inflammatory process, the vascular system undergoes marked changes such as vasodilation and increased endothelial permeability. Bradykinin, an important mediator of inflammation, contributes to these changes through activation of the bradykinin B1 and B2 receptors and subsequent activation of nitric oxide (NO) generating enzymes, known as nitric oxide synthases (NOS). At present, many investigators have focused on the pro-inflammatory effects of inducible nitric oxide synthase (iNOS), but little research has been done to investigate the role of endothelial nitric oxide synthase (eNOS) during an inflammatory response. We have evidence that suggests that B2 receptor signaling differs in control and cytokine-treated human lung microvascular endothelial cells (HLMVECs). Our goal is to delineate the signal transduction pathway of the B2R that leads to NO production in cytokine-treated

endothelial cells. With the use of specific pharmacological inhibitors and with access to a porphyrinic microsensor, we have collected data that suggests that the B2R couples to  $G_{i/o}$ , signals through Src and mitogen-activated protein kinase (MEK) and ultimately results in prolonged NO generation. We are currently investigating how these signaling components induce prolonged eNOS activation.

### **Ram Naikawadi (R. Ye)**

My work is directed towards understanding the mechanism of sepsis-induced Acute Lung Injury (ALI) or Acute Respiratory Distress Syndrome (ARDS). In septic patients, multiple organ failure, predominantly lung injury is the cause of death. During the invasion of pathogenic microbes, PMNs (Polymorphonuclear Leukocytes) are the first line of host defense. Chemoattractants released by the microbes attract the PMNs towards the site of infection. PMNs have the microbicidal molecular machinery in the form of NADPH oxidase which produces superoxide anions. But, uncontrolled activation of the NADPH oxidase results in injury to the host tissue. Therefore, proper regulation of this enzyme is a necessity. A PIP3-dependent Rac GEF (Guanine Nucleotide exchange factor), is known for its role in mediating chemoattractant-induced superoxide production along with other NADPH oxidase components in PMNs. In the next couple of years, I would like to focus on understanding the role of this GEF and dissect its mechanism in sepsis-induced acute lung injury.

### **Kelly O'Brien (X. Du)**

Platelets are critical for the maintenance of hemostasis, but under pathological conditions, can also contribute to thrombosis. Platelet activation is required for platelets to adhere to subendothelial matrix proteins at sites of vascular injury and to promote platelet aggregation. Elucidation of the signaling pathways regulating platelet activation is essential for the identification of novel anti-thrombotic targets for the prevention of thrombosis, a major cause of heart attack and stroke. It is established that Phosphoinositide(PI)3 Kinases play important roles in platelet activation. Akt, Protein Kinase B, the most well known effector of PI3 Kinases, has been shown to be activated by various platelet agonists. Akt is a serine/threonine kinase with three isoforms: Akt1, Akt2, and Akt3. Akt has been implicated in cell cycle regulation, growth, development, migration, proliferation, and metabolism. It has been demonstrated that platelets express Akt1 and Akt2. Knockout of Akt1 or Akt2 in mice exhibit defects in platelet function, suggesting Akt1 and Akt2 have stimulatory roles in promoting platelet activation. Preliminary data from our lab indicates Akt3 is also expressed in platelets. My project is focused on the characterization of Akt3 in platelet function. I am also interested in determining how Akt isoforms stimulate platelet activation, specifically, the role of Akt isoforms in regulating the Nitric Oxide-cyclic GMP-Protein Kinase G pathway.

### **Tracy Thennes (D. Mehta)**

Acute lung injury (ALI), characterized by capillary barrier dysfunction, is associated with high morbidity/mortality and has no effective therapy. The endothelial barrier is maintained by adherens junctions and cell-extracellular matrix interactions, called focal adhesions. We showed focal adhesion kinase (FAK), a non-receptor tyrosine kinase is required to maintain endothelial barrier integrity and restore barrier function following injury by the inflammatory mediator, thrombin. Sphingosine-1-Phosphate (S1P) is an endogenous bioactive lipid that ligates its receptor, S1P1, to strengthen the endothelium by organizing intracellular and cell-matrix adhesion. My research projects involve assessing the role of endothelial FAK in regulating ALI and how FAK cross-talks with S1P1 to maintain lung vascular barrier integrity. I will use inducible-endothelial specific FAK deleted mice, which I generated recently, along with sophisticated cell imaging, biochemical and physiological techniques to address my hypotheses.

### **Emily Vandembroucke (A. Malik)**

The endothelium is a semi-permeable barrier that lines all blood and lymphatic vessels in the body and regulates the exchange of fluid and solutes between blood and surrounding tissue. Endothelial cells form contacts with surrounding cells primarily through adherens junctions, which can be regulated to alter the permeability of the endothelial barrier. Circulating inflammatory agents trigger signaling cascades in endothelial cells to increase permeability through disassembly of adherens junctions. Increased permeability can lead to tissue edema, and contributes to diseases such as diabetes and ARDS. I am interested in how adherens junctions proteins interact, and what causes adherens junctions to dissociate during inflammation. Specifically, I study adherens junction proteins VE-cadherin and p120-catenin (p120). Intracellularly, p120 binds to VE-cadherin, and it has been shown that if p120 dissociates from VE-cadherin, VE-cadherin internalizes into the cell, and the adherens junction falls apart. We are investigating what causes p120 to dissociate from VE-cadherin during inflammation. Our hypothesis is that PKC $\alpha$ , a serine/threonine kinase, phosphorylates p120, which causes p120 to dissociate from VE-cadherin. To test this hypothesis, we made point-mutations in p120 at the phosphorylation site and we express these p120 mutants into both endothelial cells and mice. We are using different techniques to observe changes in p120 association with VE-cadherin and we measure the changes in endothelial permeability caused by expression of the different mutants.

**2005**

### **Aaron Place (R. Minshall)**

The goal of my studies is to understand the mechanism of Src family kinase (SFK) inactivation in the endothelium. Literature searches have revealed that another tyrosine kinase, C-terminal Src kinase (Csk), can regulate SFK's by phosphorylation of their C-terminal regulatory tyrosine. Since Csk is not intrinsically targeted to areas of SFK localization, the roles of Cbp and Cav-1 in SFK regulation are being investigated. These two membrane adapter proteins have been implicated in coordinating Csk to sites of SFK activity in other tissues, and are also both SFK targets. The binding of Csk to phosphorylated adapters facilitates its membrane localization, as well as stimulation of Csk activity, to inactivate SFK's. So far, I have uncovered a cooperation between these two adapters to ensure negative SFK regulation, and am now investigating the molecular dynamics of Csk during this process.

### **Luiza Rusu (R. Minshall/T. Kozasa)**

#### *The Role of G $\alpha$ 12 in the Regulated Exocytosis in Human Endothelial Cells*

Endothelial exocytosis is one of the earliest responses to vascular injury and plays an important role in primary haemostasis and in inflammation. In endothelial cells, thrombin activates G protein-coupled receptors, leading to exocytosis from the Weibel-Palade bodies storage pool.

Heterotrimeric G proteins from G12 family were implicated in regulated exocytosis via cell cytoskeleton rearrangements in PC12 cells and in platelets. Our laboratory showed that the  $\alpha$  subunit of G12 interacts with  $\alpha$ SNAP, an adaptor protein which is required for membrane fusion. Our published data indicate that G $\alpha$ 12 plays a role in membrane trafficking in endothelial cells, thereby revealing novel G $\alpha$ 12 signaling pathway.

Our preliminary data indicate that activated G $\alpha$ 12 enhances von Willebrand factor release from Weibel-Palade bodies in human endothelial cells. My project is aimed at understanding the mechanisms of the G $\alpha$ 12-regulated exocytosis in endothelial cells.

### **Katy Wong (J. O'Bryan)**

Our lab focuses on the multi-domain scaffolding protein intersectin (ITSN). ITSN's multiple modular domains suggests that it plays a role in signal transduction, and indeed ITSN has been link to endocytosis, GTPase regulation, transcription and receptor down regulation. My project focuses on how ITSN spatially and temporally regulates all of these pathways. One technique that I am taking advantage of to address this issue is bimolecular fluorescence complementation (BiFC). BiFC takes advantage of the observation that YFP can be split into amino- and carboxyl-terminal fragments, neither of which is fluorescent. However, when these fragments are fused to two proteins that interact, the interaction results in reconstitution of the fluorescent protein. This technique allows for the temporal and spatial monitoring of protein:proteins interactions in live cells. Using this technique among others I hope to further elucidate ITSN's role as a signal integrator.

**2004**

### **Crystal (Zoe) Hoepfner (R. Ye)**

My current research project involves the arrestin family of proteins, primarily the non-visual arrestins or  $\beta$ -arrestins. Classically recognized for their role in "arresting" or terminating G protein coupled receptor signaling, the  $\beta$ -Arrestins have more recently been recognized as important scaffolds for many signaling cascades, including the MAPK and NF- $\kappa$ B pathways. While both members of the  $\beta$ -Arrestin family interact with various members of these pathways they do so within different subcellular locations as  $\beta$ -Arrestin2 is excluded from the nucleus by an export signal in its C terminus while  $\beta$ -Arrestin1 is not. It is our belief that the nuclear localization of  $\beta$ -Arrestin1 is not mere circumstance but a fundamental part of its function. My goal over the next few years is to understand how  $\beta$ -Arrestin1 is involved in interacting with members of these pathways to mediate or influence gene transcription, as well as what regulates this function, including which functional portion of  $\beta$ -Arrestin1 allows for nuclear localization. Based on preliminary data it is my hypothesis that  $\beta$ -Arrestin1 has a unique role in directly influencing transcription in the nucleus.