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The Beat Newsletter

College of Medicine

The Beat

University of South Alabama
College of Medicine

July 1999

REMODELING THE MAMMARY GLAND AT THE TERMINATION OF BREAST FEEDING: ROLE OF A NEW REGULATOR PROTEIN BRP39

How could a sugar polymer called "chitin" that occurs naturally in shrimp and crab shells act positively to help remodel the mother's breasts at the end of breast feeding, yet at other times become involved in breast cancer pathology? This question might not seem to have an obvious connection to ***DR. NATHAN ARONSON'S, (Lenoir Locke Professor and Chair of Biochemistry and Molecular Biology)*** *main research focus, which for more that three decades has been the process whereby cells breakdown glycoproteins.*

Glycoproteins are important biological copolymers that consist of both carbohydrate and protein and their degradation is catalyzed by hydrolytic enzymes. One of the enzymes discovered in Dr. Aronson's laboratory termed "chitobiase" can also breakdown chitin, a pure carbohydrate polymer that helps form the molecular skeleton of both insects and crustaceans. Next to cellulose, chitin is the most abundant polysaccharide in the biosphere. Both of these sugar polymers are long and flat, and this useful shape explains why nature has put them to extensive architectural use as "molecular boards".

A few years ago Dr. Aronson was analyzing the amino acid structure of the chitobiase enzyme they had discovered. A computer search of the available database of protein and enzyme sequences revealed a large group of similar chitin-hydrolyzing enzymes. What caught Aronson's eye, however, was an additional small set of structurally similar proteins that had one important change: these could not catalyze chitin digestion. Among the almost 400 amino acids that make up a normal chitinase enzyme, nature had substituted for one crucial acid residue preventing these novel proteins from hydrolyzing the polysaccharide. Little is known about the physiological function of these inactive chitinase-related proteins, but based on their structure they might likely bind a chitin-like polysaccharide or glycoprotein. This molecular event would then help regulate various kinds of tissue remodeling and/or differentiation. For example, one of these proteins only appears during wound repair in cartilage, while a second works during the earliest events of pregnancy when a newly fertilized ovum is implanted in the oviduct. A third member of the chitinase-related protein group was discovered at Harvard University by scientists studying specific types of cancer cells from the mammary glands of mice. The protein was named BRP39. This abbreviation designates the tissue, time of occurrence, and size of the protein [B(*breast*)R(*regression*)P39(*protein of 39,000 molecular weight*)]. Not only does BRP39 appear in unique types of breast cancer cells, but these scientists also found it is expressed by the normal gland once the young mouse pups are weaned from their mother at the termination of breast feeding. The latter physiological stage is called *involution*, a period when the breast not only stops producing the unique proteins and nutrients that form the mother's milk, but also the time in which the structure and function of the gland must revert back to the nonpregnant state. Dr. Aronson's major initial goal is to determine the exact role that BRP39 has in this remarkable physiological process. Other scientists have already reported many important biochemical details for the chitinase enzyme, and these data are being used to help us characterize similar molecular information about BRP39, especially the nature of its predicted chitin-binding domain.

Fig. 1 *Top view of a computer model for a chitin fragment (shown by space-filling atoms) bound in the active site groove of a chitinase. The model is being used to predict the binding mode for BRP39.*

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Once it is learned how BRP39 acts during the normal process of mammary gland involution Aronson's research team plans to use this information to help reveal its behavior in the breast cancer cells where it was initially discovered. His initial hypothesis is that BRP39 acts normally as a protective signaling factor that determines which cells are to survive the drastic tissue remodeling that must occur during involution. Thus, many breast epithelial cells which have been increased in number during pregnancy [in preparation for breast feeding] must now be destroyed. These cells die by a precise programmed cell death pathway called "*apoptosis*", but most of the breast tissue remains viable, and we think BRP39 contributes to regulating which cells in the gland are to survive. There is good evidence that BRP39 is secreted by breast epithelial cells, and therefore its signaling activity may involve either carbohydrate-containing molecules in the extracellular matrix or cell surface glycoproteins.

One could easily imagine that certain cancers could surreptitiously utilize the proposed normal "protective signaling" by BRP39 in order to extend their own survival and thereby allow them to invade the organ and metastasize. The type of breast cancer cells found to produce BRP39 is among the most dangerous. This class overexpresses a growth factor receptor on their cell surfaces that is called *HER-2/neu*. In human breast cancer patients, those who are positive for excess *HER-2/neu* protein have a negative prognosis for remission and survival. Up to a third of breast cancers contain extra copies of the *HER-2/neu* gene, and biotech companies have recently developed tests to measure the level of *HER-2/neu* in breast cancer patients. In late 1998, a new anti-*HER-2/neu* drug called Herceptin that attacks the growth factor receptor was approved by the FDA. So far it has shown positive therapeutic results, especially when combined with a chemotherapeutic agent like Taxol.

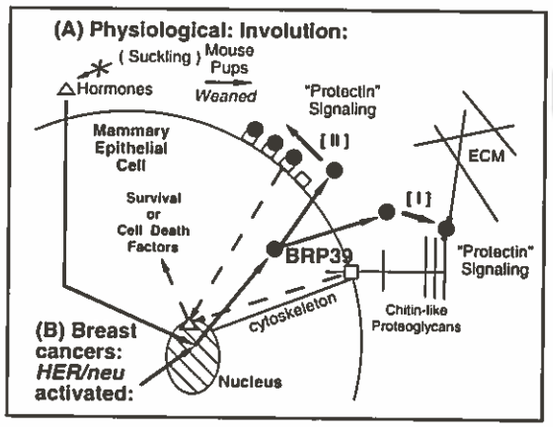


Fig. 2 Proposed pathways by which BRP39 is induced (A) physiologically during involution of the breast; or (B) during breast cancers caused by overexpressed growth receptor HER/neu. BRP39 upon binding either [I] to carbohydrate-containing molecules in the extracellular matrix (ECM) or [II] to cell surface glycoproteins may induce either protective effects on the mammary epithelial cells or metabolic changes that lead to cell destruction.

Dr. Aronson's research on BRP39 and the chitinases is a collaborative effort. The computer remains a very crucial experimental tool for the project. Dr. Aronson joined forces with Dr. Jeff Madura in the USA Chemistry Department who is an expert computational chemist able to predict protein structure using programs that involve advanced mathematics, physics and chemistry. In January 1999, Dr. Madura relocated to Duquense University in Pittsburgh, but maintain a joint 5-year NIH grant to support these studies on BRP39 and chitinases. Dr. Aronson's current research studies are being performed by postdoctoral scientist Dr. Katja Reichert-Poeggeler, Brian (Zeke) Halloran and medical student Kerry Griffen.

NEW PH.D. GRADUATES IN BASIC MEDICAL SCIENCES

Congratulations to the following graduates:

Hao Cheng, Ph.D.

Dissertation: "Role of Macrophages in Restricting Herpes Simplex Virus Type I Growth After Ocular Infection"
Major Professor: Dr. Robert N. Lausch, Department of Microbiology and Immunology

Mark S. Taylor, Ph.D.

Dissertation: "Modulation of Vascular Smooth Muscle Contraction by Cyclic Nucleotides: Calcium-Dependent and Independent Mechanisms"
Major Professor: Dr. Joseph N. Benoit, Department of Physiology

Jianguo Xu, Ph.D.

Dissertation: "Effects of Ischemic and Hypoxic Preconditioning on Cardiomyocyte Apoptosis"
Major Professor: Dr. T. Michael Fan, Department of Pharmacology.

UNIVERSITY OF SOUTH ALABAMA COLLEGE OF MEDICINE
CLASS OF 1999 RESIDENCY APPOINTMENTS

NAME	*MEDICAL CENTER*	*DISCIPLINE*
Robert K. Barnett	University of South Alabama, Mobile, AL	General Surgery
Gregory Damon Borak	Medical University South Carolina, Charleston, SC	Internal Medicine
Ronald F. Borlaza	University of Alabama, Birmingham, AL	Internal Medicine
Jason Keith Burrus	University of Alabama, Birmingham, AL	Urology
William A. Carroll, Jr.	University of Arizona, Tucson, AZ	Pathology
Sharon B. Chaney	Baptist Health System, Birmingham, AL	Pathology
Edward Chung	Wake Forest University, Winston-Salem, NC	Internal Medicine
Christopher D. Connolley	Vanderbilt University, Nashville, TN	Internal Medicine
Eugenie Lynn Crawford	University of Kentucky, Lexington, KY	Internal Medicine
Julie Marshall Dennis	University of Alabama, Birmingham, AL	Pediatrics
Matthew Michael Eves	University of South Alabama, Mobile, AL	Internal Medicine
Priscilla G. Fowler	University of Alabama, Birmingham, AL	Ophthalmology
Kevin Michael French	Naval Medical Center, Portsmouth, VA	Medicine
Otis Gowdy, Jr.	University of Mississippi, Jackson, MS	Internal Medicine
Bryan Thames Green	University of South Alabama, Mobile, AL	Internal Medicine
Anthony Scott Greer	University of South Alabama, Mobile, AL	Medicine-Pediatrics
Leigh Allison Haden	University of South Alabama, Mobile, AL	Pediatrics
Anthony M. Harton	Beth-Israel Deaconess, Boston, MA	Pathology
Don Elliott Heinkel	St. Elizabeth, Appleton, WI	Family Practice
Burritt William Hess	Valley Baptist Medical Center, Harlingen, TX	Family Practice
Robert Neil Honea, Jr.	Selma Family Medicine, Selma, AL	Family Practice
Tamera K. Hughes	University of South Alabama, Mobile, AL	Radiology
Bradford H. Jones	University of Alabama, Birmingham, AL	Internal Medicine
Marirose C. Jordan	University of South Alabama, Mobile, AL	Family Practice
Kevin Reid Katona	Tuscaloosa Family Practice, Tuscaloosa, AL	Family Practice
David McRae Kitchens	University of Cincinnati Hospitals, Cincinnati, OH	Urology
Andrew Wayne Knott	University of Cincinnati Hospitals, Cincinnati, OH	General Surgery
Rupa V. Kothandapani	University of Cincinnati Hospitals, Cincinnati, OH	Urology
Aryanna Fey Lee	Sacred Heart Hospital, Pensacola, FL	Pediatrics
Jose Andres Martinez	Miami Children's Hospital, Miami, FL	Pediatrics
Elizabeth P. McBay	Keesler AFB Medical Center, Biloxi, MS	Medicine
Bruce M. McClenathan	Tripler Army Medical Center, Hawaii	Medicine
Bryan Andrew McCluer	University of South Alabama, Mobile, AL	General Surgery
Mary Ellen McHargue	University of Texas, Houston, TX	Anesthesiology
Tammy K. McLean	Medical College Georgia, Augusta, GA	Dermatology
Brenda C. Miller-Edmonson	University of Tennessee, Memphis, TN	Ophthalmology
Darryl Mueller	Louisiana State University, New Orleans, LA	Otolaryngology
Farinna L. Myers-Willis	Medical College of Ohio, Toledo, OH	Obstetrics-Gynecology
Anita Nanda	University of Alabama, Birmingham, AL	Pediatrics
Christopher E. Nicholls	University of Cincinnati Hospitals, Cincinnati, OH	Obstetrics-Gynecology
Brian David Patz	University of Arkansas, Little Rock, AR	Pediatrics
Thomas Bartley Pickron, Jr.	Georgia Baptist, Atlanta, GA	General Surgery
Reagan Ponder	University of Hawaii, Honolulu, HA	Obstetrics-Gynecology
Dina Ragheb	Louisiana State University, New Orleans, LA	Radiology
Seth David Rayburn	University of South Alabama, Mobile, AL	General Surgery
Lezlie T. Reed-Johnson	University of Alabama, Huntsville, AL	Family Practice
Lenore L. Rosa	University of South Alabama, Mobile, AL	Family Practice
Dina Mache Ruffin	University of Mississippi, Jackson, MS	Pediatrics
Stephen Wilbon Russell	University of Cincinnati Hospitals, Cincinnati, OH	Medicine-Pediatrics
Omar Shadman	University of Texas, Houston, TX	Anesthesiology
Denzil Lester Sockwell	University of South Alabama, Mobile, AL	Medicine-Pediatrics
Joseph Hare Sugg, Jr.	University of Tennessee, Chattanooga, TN	Ophthalmology
Michelle Jackson Sumrall	University of South Alabama, Mobile, AL	Pediatrics
Amy Michelle Thompson	University of Kentucky, Lexington, KY	Obstetrics-Gynecology
Darren Keith Waters	University of Kentucky, Lexington, KY	Emergency Medicine
Jacob Bond Webster	University of Alabama, Birmingham, AL	Medicine-Pediatrics
Dylan Robert Wells	University of Tennessee, Memphis, TN	Obstetrics-Gynecology
Brett J. Widick	East Tennessee State University, Johnson City	Family Practice
Michael Clay Williams	Memorial Medical Center, Savannah, GA	Family Practice

HONORS CONVOCATION AWARDS

Dean's Award ..... Jason Keith Burrus
Robert Neil Honea, Jr., Denzil Les Sockwell, III
Darren Keith Waters, Jacob Bond Webster

Awarded to the graduating seniors who have accumulated the highest scholastic grade point average for the full four years of medical school.

Pharmacology Achievement Award ..... Robert Neil Honea, Jr.
Jacob Bond Webster

The award is designed to recognize outstanding student performance in Pharmacology.

John W. Donald Memorial Award in Surgery ..... Jacob Bond Webster

Awarded to the senior student who best demonstrated clinical and academic excellence in the surgery clerkship.

Hollis J. Wiseman Award for Excellence in Pediatrics ..Jacob Bond Webster

Presented to the student who best exemplified Dr. Wiseman's outstanding scholarship, compassion for patients and families, involvement in the profession and community, enthusiasm for exploration and steadfast love of family, friends and colleagues.

Obstetrics/Gynecology Award ..... Robert Neil Honea, Jr.

Presented to the graduating medical student who, through scholarship, patient care, interaction with faculty and house staff, and motivation, has demonstrated excellence in Obstetrics and Gynecology.

Outstanding Student in the Anatomical Sciences ..... Robert Neil Honea, Jr.

Awarded by the faculty of the Department of Structural and Cellular Biology to the student with the best performance in the four anatomical science courses.

Excellence in Emergency Medicine ..... Darren Keith Waters

The Excellence in Emergency Medicine award is given by the faculty of the Department of Emergency Medicine and the Society of Academic Emergency Medicine to the student demonstrating outstanding clinical skills and proficiency in Emergency Medicine.

Charles W. Urschel Achievement Award in Physiology ..... Rupa Virupaksha Kothandapani
Darren Keith Waters

Awarded to a graduating senior for outstanding performance in the Physiology course and/or Physiology research.

American Medical Women's Association Scholarship Achievement Citation ..... Rupa Virupaksha Kothandapani

Presented to those women students who graduate in the top ten percent of their class.

Neurology Award ..... Andrew W. Knott

Awarded by the Department of Neurology to a senior student who has shown excellence in clinical neuroscience.

Lange Award ..... Andrew W. Knott

Awarded by vote of the faculty to a senior student with superior academic achievement.

Merck Award in Ophthalmology .... Priscilla Goodwyn Fowler
Brenda Carol Miller-Edmonson
and Joseph Hare Sugg, Jr.

Awarded to the graduating medical student, selected by the Ophthalmology faculty, who demonstrated both an interest in ophthalmology and best exemplified our ideal of competent and compassionate patient care.

Community Service Award ..... Stephen Wilbon Russell

This award is presented by the Medical Society of Mobile County to a senior whose classmates believe best fulfills the ideals of humanitarian public service as demonstrated by superior awareness of, and achievement in, civic and community programs.

Honors Award in Biochemistry ..... Ronald Frederick Borlaza

Awarded to a student who excelled in all aspects of the Medical Biochemistry course.

Family Practice and Community Medicine Student Award ..... Marirose Cantagallo Jordan

Awarded by the faculty of the Department of Family Practice and Community Medicine to the graduating senior student who shows the greatest potential as a future family physician. The selection is based on the student's broad general medical knowledge and clinical skills, demonstration of concern for the physical, emotional and social well-being of patients, and understanding of concepts central to family medicine.

Pathology Award ..... Anthony Millard Harton
Lenore Landers Rosa

Given jointly by the Alabama Association of Pathologists and the University of South Alabama Department of Pathology faculty and residents for excellence in Pathology.

Merck Award ..... Anthony Millard Harton
and Bryan Thames Green

Awarded by vote of the faculty to senior students with superior academic achievement.

Samuel Eichold Award ..... Bryan Thames Green

Presented to the graduating medical student who through scholarship, patient care, interaction with faculty and housestaff, and motivation has demonstrated outstanding achievement in Internal Medicine.

Medical Alumni Leadership Award ..... Christopher Eugene Nicholls

Awarded to a senior student, by vote of classmates, in recognition of outstanding leadership of the graduating class.

SNMA Leadership Award ..... Otis Gowdy, Jr.

Awarded by the Student National Medical Association to a graduating senior who has demonstrated outstanding community, school and organizational service and leadership qualities.

Mutual Assurance Award ..... Anthony Scott Greer

This award is presented to a senior medical student who plans to remain in Alabama for residency and who excels in patient communication.

NEW TOOL IN HEART DISEASE FIGHT

The University of South Alabama has a new tool, called **Angiojet**, to fight coronary heart disease. Cardiologist **DR. JACK PAINTER** recently become the first physician in southern Alabama to use the device in patients. The device was used in one patient with a heart attack to remove a clot in a coronary vessel and in a second patient with an occluded artery in the leg.

In addition to treating blockages in the heart and legs, Angiojet has been used to treat clots in shunts used in dialysis patients, which are prone to develop blockages.

BARIK RECEIVES BURROUGHS WELLCOME MALARIA RESEARCH AWARD

Sailen Barik, Ph.D., Assistant Professor of Biochemistry and Molecular Biology, has received a two-year $100,000 Burroughs Wellcome Award in the field of "New Initiatives in Malaria Research". This award is made to only a small number of researchers who were nominated by their sponsoring institutions.

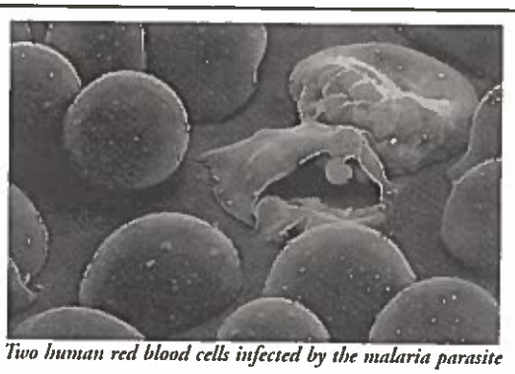
The Greek physician Hippocrates (5th Century BC) was the first to describe the characteristic symptoms of a malaria infection: intermittent and often relapsing fever, accompanied by drenching sweats and shaking chills. Centuries later, the medical almanac of 1888 referred to malaria as "one of the great scourges of humanity", wreaking havoc in civilizations, and claiming more lives than any other infectious disease. Even today, malaria kills nearly 1.5 million people, mostly children, throughout the world. Although malaria has been relatively rare in the Northern United States, the hot and humid South has seen many cases over the years. In fact, it was rather common in the Springhill area of Mobile not too long ago. Worldwide, 2.2 billion people (40% of the planet's population) are now in danger of contracting malaria.

Malaria is caused by protozoan parasites called *Plasmodia*, spread by female *Anopheles* mosquitoes through blood bites. Eradication of mosquitoes by DDT, hailed as the wonder pesticide of the post-WWII era, and the worldwide use of anti-malarial drugs of the quinine family led to a temporary eradication of malaria in many places, until the parasites and the mosquitoes struck back. Natural mutations produced drug-resistant *Plasmodia* as well as DDT-resistant mosquitoes, resulting in a resurgence of malaria. It is estimated that nearly 80% of all parasites in malaria-infected areas are now resistant.

Dr. Barik explains that "in rural Bengal, India, where he grew up (not far from Calcutta, a city that has produced five Nobel Laureates including Mother Teresa and ironically, the 1902 Laureate Sir Ronald Ross, who discovered how the malaria parasite is transmitted by the mosquitoes), malaria used to reign supreme before the second World War. Dr. Barik still remembers in the sixties Government health workers (call them "mosquito-busters" if you will) used to come to his village once a year, asking them to vacate their houses, and spraying DDT literally all over the place. Of course, within five years, DDT began to appear in every member of the food chain: from water and soil to plants, fish, and falcon eggs, and even in human milk. The grave for DDT was dug. It was banned all over the world, and the mosquitoes invited their *Plasmodia* friends to the victory party that is still going on !"

The realization that resurgent malaria is a global issue has called for renewed strategies, and in response, all major national and international organizations have joined forces. These include: National Institutes of Health, World Health Organization, Center for Disease Control and Prevention, and the Wellcome Foundation (UK) and Burroughs-Wellcome Fund (USA), to name a few. The malaria genome project, operated by a multinational consortium, is running at full steam, and the sequencing of chromosome 2 (out of a total of 14) is already completed.

Since conventional antimalarials have limited success and no effective vaccine is available yet, Dr. Barik's laboratory began studying the basic signaling mechanisms of this parasite. The parasite goes through a number of "stages" in the blood and spleen in its long life cycle, and no one knows how one stage progresses into another. However, based on Barik's extensive knowledge in other species, it was logical to assume that phosphorylation of proteins would be a major mechanism in such regulations. These reactions are reversible, and enzymes that catalyze them are called kinases and phosphatases.



Two human red blood cells infected by the malaria parasite

In the malaria parasite, however, these molecules have remained undiscovered. Dr. Barik's immediate goal, therefore, is to identify these key enzymes and then determine their exact roles in the transition and signaling between the parasitic stages and the interactions between the parasite and the host. Dr. Barik states that the Burroughs-Wellcome Fund (BWF) Award is a

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recognition of the novelty of their strategy and good "track-record" in this general area of research. The BWF Award is exciting news to the small but top-quality parasitology community in the College of Medicine. Dr. Barik is particularly thankful to Dr. Stephen G. Kayes, an internationally recognized parasitologist and an editor of the Journal of Parasitology, for his advice and support throughout the years. Barik's research has also benefited from collaboration with Dr. Alan Fairlamb of the University of Dundee, Scotland, and Dr. Debopam Chakrabarti of University of Central Florida, Orlando. Two key researchers in Dr. Barik's laboratory were instrumental in launching this project early on: graduate student Sean Dobson and medical student Takiko May who worked in the summer of '97. They received help from Toshihiro Ansai, D.D.S., Ph. D., a visiting scientist on a sabbatical leave from Kyushu Dental College, Japan.

Mr. Dobson's research has shown the existence of at least 8 different phosphatases, their physiological inhibitors and substrates, and potentially novel forms of regulation. Dr. Barik states, "moreover, for the first time we have a clue as to how the parasite develops resistance against cyclosporin, an otherwise effective antiparasite drug that is also widely used to suppress the immunity of transplant patients to prevent their rejection of the donor tissue. Cyclosporin was found to inhibit an essential phosphatase of the parasite, and the parasite probably retaliates by mutating the phosphatase to a cyclosporin-resistant form." Future studies, therefore, may allow the design of a class of second-generation cyclosporins that will inhibit the mutant form of phosphatase.

Some of Dr. Barik's research was presented at the annual Molecular Parasitology Symposia in Woods Hole, MA. It is now clear that research generated by the BWF award will most certainly lead to a better understanding of essentially every aspect of parasitic behavior, such as how it invades the red blood cells and then eats the hemoglobin and glucose, how it is killed in the spleen, and how it produces the chill and the fever. As exemplified by the cyclosporin study, many of Dr. Barik's findings may eventually lead to effective antimalarial drugs that would target the parasitic molecules involved in these key processes.

If you would like to submit an article for publication, please forward it to:

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FAX (334) 460-6073
Visit "*The Beat*" at
http://southmed.usouthal.edu/com/thebeat.htm

Faculty News...

Mark S. Brown, M.D., Director of Ocuplastic Surgery, Department of Ophthalmology, was presented the Physician Recognition Award by the American Medical Association for continuing medical education.

Dr. Brown, who specialized in Plastic and Reconstructive Surgery of the Eyelid, Orbit and Lacrimal System, was recently recognized and interviewed by Ocular Surgery News for his use of websites in Ophthalmology and Medicine. His website at: www.EyePlastics.com, provides educational information to patients and physicians on ophthalmic plastic surgery.

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Miguel Pappolla, M.D., associate professor of pathology, has been named to the editorial board of the "Journal of Neuropathology and Experimental Neurology," He has also been named associate editor of "Journal of Alzheimer's Disease."

Dr. Pappolla has been recognized nationally and internationally for his research contributions to Alzheimer's disease.

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Leonard Rich, M.D., professor and chair of ophthalmology, was named an honorary fellow at the annual meeting of the Louisiana-Mississippi Ophthalmological Society. Dr. Rich made presentations entitled "Vitamins, Nutrition in Ophthalmology" and "Thyroid Ophthalmology: Two Is Not Always Better Than One" at the meeting.

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Mary Townsley, Ph.D., professor of physiology, has been accepted as a member of the 1999-2000 Class of fellows in the Hedwig van Ameringen Executive Leadership in Academic Medicine (ELAM) Program for Women. The candidates represented almost 60 respected academic institutions from across the U.S. During the program, ELAM fellows will work together with eminent faculty and national leaders to find innovative ways of implementing the positive changes in leadership that are necessary to recast and reconfigure academic health centers and, ultimately, health care for the 21st century.

COMMUNITY AWARENESS MEETING

The USA Cancer Center will present a program on "Breast Cancer Prevention and Treatment Updates" at the Mobile Gas Auditorium on Wednesday, July 28, 1999 at 7:00 pm. This program is free and open to the public. Refreshments will be served. For more information call 460-7405.

HOW UNIVERSITIES GET LICENSES FOR HUMAN EXPERIMENTS

The federal Office for Protection from Research Risks issues and monitors licenses for universities where research on human subjects is conducted. The O.P.R.R. has issued more than 3,000 licenses, known as Single Project Assurances, that allow a university to conduct a single study. The office has also given about 430 licenses, known as Multiple Project Assurances, to major research universities to cover large volumes of research over five years.

Process for a Single-Project License

A scientist applies for a grant from a federal agency to finance a proposed research project.

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The federal agency convenes a committee of scientists to evaluate the proposal's scientific merit.

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The federal agency tentatively awards a grant. At the National Institutes of Health, the largest source of federal grants for biomedical research, 33 per cent of proposals win grants.

↓

The approved project is examined by an Institutional Review Board (I.R.B.) On the scientist's campus. The panel of physicians, scientists, and community representatives focuses solely on protecting human subjects of research. It makes sure that studies that include people who may be particularly vulnerable - such as minors, pregnant women or the mentally ill - would not harm or exploit those subjects.

↓

The I.R.B. approves, rejects, or recommends changes in the project's human-subject proposal before the federal agency will release the grant funds.

↓

Officials at the scientist's institution sign a contract with the O.P.R.R. - known as a Single Assurance - agreeing to follow federal rules on the protection of human subjects in research. The contract acts as a license allowing institutions to use federal grants for human-subject research.

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Grant funds are released.

↓

Research begins.

↓

The IRB must check on the study once a year and report to the O.P.R.R. anything unexpected that happens to research participants. In particular, the IRB. is required to report "adverse events," such as the death of a subject when no risk of that was foreseen, or the passing out of a subject when no risk of losing consciousness was expected.

Process for a Multiple-Project License

An institution negotiates a three-year license with the O.P.R.R. to receive federal funds for various research projects. (After the first three-year period, the license is renewable every five years.)

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A scientist applies for a grant from federal agency to finance a proposed project.

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Within 60 days of submission to the federal agency, the proposal must be reviewed by the I.R.B. at the scientist's institution.

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The IRB approves, rejects, or recommends changes in the project's human-subject protections. The IRB approval precedes the release of grant funds.

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The federal agency reviews the proposal for scientific merit.

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The federal agency decides whether to award a grant.

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If it decides to do so, grant funds are released.

↓

Research begins.

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The I.R.B. must check on each study once a year and report to the O.P.R.R. any "adverse events" or other unexpected complications that affect research participants.

MEDICAL INFORMATICS
FOR FACULTY DEVELOPMENT

Free netscape training materials created with physicians, medical students, residents and medical school faculty and staff in mind can be located at http://pilot.msu.edu/user/inetproj/homepage5.html. These files are in .pdf format and can be read and downloaded on any computer with a web browser and the Adobe Acrobat Reader. In addition to the Netscape files are an annotated bibliography of articles pertaining to the Internet and medicine, and a set of links to medical resources.

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