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The Beat



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PROBING THE MOLECULAR STRUCTURE OF MITOCHONDRIAL TRANSPORT PROTEINS

Research in the laboratory of Dr. Ronald S. Kaplan, a professor in the Department of Pharmacology, focuses on elucidating the mechanisms of action of mitochondrial transport proteins at the molecular and atomic levels. These carriers are responsible for the high-magnitude flux of metabolites which occurs across the mitochondrial inner membrane and is required in order to supply the cell with ATP made via oxidative phosphorylation.

Kaplan's interest in mitochondrial transporters originated during his graduate studies at New York University in the laboratory of Dr. Peter S. Coleman. "I initially became interested in studying transport because I was intrigued with the idea of communication between intracellular compartments via the movement of metabolites across membranes. In those days, we studied transport at the level of isolated mitochondria. We sought to define, characterize, and study the effect of disease on transporter function. The technologies for molecular studies into transporter function were for the most part simply not yet available". Kaplan's Ph.D. thesis focused on characterizing citrate transport in mitochondria isolated from different types of tumors. During subsequent postdoctoral training in Dr. Pete Pedersen's laboratory at The Johns Hopkins School of Medicine, Kaplan learned the approaches and techniques for studying transporter function at the molecular level. During this period of time he developed methods for purifying and reconstituting the mitochondrial phosphate and dicarboxylate transport proteins. The functional properties of the purified transporters were then studied in liposomal systems. "This was an exciting period because for the first time investigators were able to clearly demonstrate that single proteins were in fact responsible for the transport functions observed in isolated mitochondria. Also, with the purified protein in hand, we could now explore the role of individual amino acid residues in transporter function".

In 1986, Kaplan moved to the University of South Alabama College of Medicine as an Assistant Professor in the Department of Pharmacology. Kaplan then combined his training on protein purification with his earlier interest in the mitochondrial citrate transporters, and in studies spearheaded by June A. Mayor, an experienced collaborator, the laboratory developed the first procedure for obtaining significant quantities of highly purified, functional citrate transport protein. Subsequent to this work, Dr. David Gremse, a colleague in the Department of Pediatrics with a keen interest in transporter research joined the Kaplan laboratory on a part-

time basis in 1990. Working with the purified transport protein and a lysine-selective covalent modifying reagent, Dr. Gremse, with the assistance of Brenda Dean, a Research Technologist, demonstrated that the substrate binding site within the citrate transporter contained an essential lysine residue(s). During the same period of time, the laboratory became interested in examining the effect of diabetes on mitochondrial transporter function. In collaboration with Dr. Glenn Wilson of the Department of Structural and Cellular Biology, Kaplan, with the assistance of Luanne Oliveira, a Research Technologist, and others in the laboratory, showed that the function of three different mitochondrial transporters was altered in type 1 diabetes, and that these changes supported the underlying hypothesis that mitochondrial transporter function is regulated in coordination with the enzymes of metabolic pathways to which they either supply substrate or remove product. Furthermore, the diabetes-induced changes could be reversed by insulin therapy, thereby providing the first evidence of a role for insulin in the regulation of these carriers. According to Kaplan, "we view diabetes as an excellent model system that allows us to either up or down regulate transporter function at will, and this should now enable us to investigate the molecular mechanisms by which these transporters are regulated".

In order to probe the role of individual amino acids in the mechanism of the citrate transporter, it soon became apparent that the tools of molecular biology would be needed. Thus, in 1992, Kaplan did an "in house" sabbatical in Professor David Wood's laboratory in the Department of Microbiology and Immunology. This collaboration led to the first elucidation and analysis of the primary structure of the mitochondrial citrate transport protein from any source. Following this work, studies in Kaplan's laboratory carried out by Yan Xu, a graduate student, led to the development of a system for expressing abundant quantities of the rat liver citrate transport protein. "This was a remarkable breakthrough because now for the first time we could obtain sufficient quantities of purified transporter (i.e., 10-100 mg of transport protein) to enable a variety of structure studies that were heretofore impossible". Mayor and Gremse then utilized this system to identify the gene that encodes the yeast mitochondrial citrate transporter via overexpression and a functional characterization approach to directly identify the transport function that is encoded by a given gene. In 1994 Dr. David Kakhniashvili, a Research Associate, joined the laboratory

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and together with others in the laboratory utilized this approach to identify the yeast gene which encodes the mitochondrial dicarboxylate transporter. This work provided the first information on the primary structure of this metabolically important transporter from any organism.

Currently, the laboratory is following a three pronged approach in order to elucidate the structural basis underlying citrate transporter function. Yan Xu is overexpressing site-directed mutated forms of the citrate transporter in order to identify essential residues and to begin mapping the substrate translocation pathway through the carrier. In collaboration with Dr. David Nelson, a yeast molecular geneticist at the University of Tennessee, the laboratory has recently created a yeast knockout strain in which the chromosomal copy of the citrate transporter gene has been deleted. The knockout strain will then be used as a host to express mutated forms of the transporter in a more "physiological" environment. Finally, in collaboration with R. Michael Garavito at the University of Michigan, they are attempting to crystallize the transporter so that X-ray diffraction analysis can be used to obtain high-resolution structural information. Kaplan recently received a new four-year grant award totaling \$805,361 from the National Institutes of Health to support this work.

According to him, "One of the great joys of research is learning new approaches and developing new expertises by collaborating with experts in different areas so that a multiplicity of strategies and technologies can be applied to the problem at hand. The progress during the last 20 years in the area of mitochondrial transport has been immense and it seems that we are on the verge of understanding how these proteins function at the atomic level. An elucidation of the structural basis underlying transporter function (at high resolution) has not yet been obtained for any metabolite transporter, and thus we believe solving this problem will represent a major scientific breakthrough". Dr. Kaplan and his colleagues are poised to accomplish this goal.

LIONS/USA EYE RESEARCH GALA DINNER — A SUCCESS!

The Lions of District 34N in Alabama raised almost \$20,000 for eye research with a gala dinner celebration held October 25th at the Adam's Mark Hotel. Featured guest speaker Heather Whitestone, Miss America 1995, and spokesperson for the Helen Keller Eye Research Foundation, inspired the 500 attendees at the dinner with her story of overcoming the obstacle of her deafness to compete for and win Miss America.

The money raised will enrich the endowment for the Lions/University of South Alabama Eye Research Institute. But, even more important than the amount of money raised, said Elton Johnson, President of the Lions/USA Eye Research Foundation, is the public recognition of the success of the Institute and of the cooperation between the Lions and the University.

Researchers at the Lions/USA Eye Research Institute are at the forefront of the battle against preventable causes of blindness. Under the scientific leadership of Drs. Steven Pittler, Robert Lausch, John Oakes and Richard Honkanen, the Institute is helping to lead the way to understanding some of the causes of retinitis pigmentosa and eye inflammations that can cause people to lose their sight. Drugs that could treat glaucoma without adverse side effects are also being studied.

The high quality of the research being done at the Lions/USA Eye Research Institute is reflected in the Cogan Award, one of eye research's

most prestigious prizes, bestowed upon Dr. Steven Pittler in 1995 for his research on gene mutations that cause retinitis pigmentosa.

Due to the huge success of the gala dinner for eye research, the institute plans to make it a regular yearly event. The city of Mobile has officially recognized the event and recorded it as Lions/Eye Research Institute day.

CONGRATULATIONS...

R. Michael Culpepper, M.D., *Director of the Division of Nephrology and Hypertension*, has been re-elected to a second term as President of Region II of the National Kidney Foundation. His election took place at the group's 46th annual meeting held in New Orleans, October 31-November 4. Dr. Culpepper will oversee the Foundation's efforts in the twelve southeastern states that comprise Region II. He will also serve on the executive committee of the National Medical Advisory Board of the Foundation.

Mark N. Gillespie, Ph.D., *Chair, Department of Pharmacology*, has accepted an invitation to serve as chairperson of the Lung Biology and Pathology Study Section of the NIH.

Shibo Li, M.D., *Assistant Professor of Medical Genetics*, has passed examinations for Boards of Clinical Molecular Genetics and Clinical Cytogenetics. Dr. Li is now certified as a Diplomate of the American Board of Medical Genetics.

J. Graham Smith, Jr., M.D., *Professor of Dermatology*, was elected to honorary membership in the American Dermatological Association during their annual meeting in September. The association is the oldest national dermatologic organization. Earlier in the year, Dr. Smith was elected to honorary membership in the American Academy of Dermatology, the largest dermatologic organization. Only five other physicians are honorary members of both societies.

McCOMBS SELECTED TO SERVE ON NIH COMMITTEE

Candace McCombs, Ph.D., *Professor of Medicine and Chief, Experimental Medicine*, was selected to serve as a member of the Peer Review Oversight Group (PROG) established by Dr. Harold Varmus, NIH Director. The group is charged with coordinating, evaluating, and making policy recommendations for the peer review process conducted at NIH. The PROG will address issues of review policy common to the entire NIH, rather than to focus on specific grant applications or study sections.

PROG is a chartered committee under the Federal Advisory Committee Act (FACA). Committee members are nominated and serve for terms of four years. Of the authorized members of the committee, six are NIH staff members and ten are representatives from the extramural community. The need for peer review to be dynamic and adaptable and to adjust to changes in science was noted as a general area in which PROG could contribute. In a time of reinvention and self-examination, NIH is seeking to make a good system better.

BASIC MEDICAL SCIENCE DEGREES AWARDED

Congratulations to —

Wesley J. Driggers: Dissertation entitled "Repair of Oxidative DNA Damage in the Mitochondrial Genome," sponsored by Dr. Glenn L. Wilson, Department of Structural and Cellular Biology.

Adrienne M. Kovacs: Dissertation entitled "Structure and Expression of the Chicken Smooth Muscle γ -Actin Gene," sponsored by Dr. Warren Zimmer, Department of Structural and Cellular Biology.

USA PHYSICIANS HELP FIVE COUPLES BECOME PREGNANT WITH NEW TECHNOLOGY

"First in Mobile area"

By using an innovative technology called intracytoplasmic sperm injection (ICSI), physicians at the USA Fertility Center have assisted five couples who previously were unable to achieve pregnancy.

ICSI was implemented last August and it involves the direct injection of a single spermatozoan into the ooplasm of an egg. "We are excited about ICSI because it produces the best pregnancy rates for patients in our community who were previously untreatable; by using ICSI in patients with male-factor disorders, we are able to inject a single sperm into an egg, achieving approximately 30 percent pregnancy for patients," explained **Botros M. Rizk, M.D.**, Assistant Professor of Obstetrics and Gynecology.

USA has seen high success rates in the couples treated with this new technique. Dr. Rizk stated "this past year we received an international award recognizing our center's technique for sperm processing. By placing high emphasis on producing high quality embryos, he expects our success rate using ICSI will continue to be above average." The ICSI procedure is supported by the University of South Alabama's full-service endocrine laboratory, located on Center Street and adjacent to USA Doctors Hospital.

THE PEDIATRIC RESEARCH OFFICE

The Department of Pediatrics and Adolescent Medicine established a Pediatric Research Office with a mission to encourage and help support clinical and basic science research activities by Pediatrics faculty. Dr. Charles Hoff was assigned a full-time role in the division with additional support provided by Drs. B. Surendra Baliga and R. Blaine Moore for basic science-oriented research activities. In addition, a full-time research nurse, Elizabeth Fillingim, B.S.N., was hired to help facilitate faculty activities in clinical research.

Historically, Pediatrics faculty involved in basic science-oriented research have had access to resources to help them conduct research

through their collaboration with colleagues in basic science departments. In contrast, initiation of clinical research by individual faculty members has been more problematic due to clinical responsibilities and lack of direct access to knowledge about funding sources, protocol development, data collection, constructing computer databases, and analytic methods. These problems (some of which were shared by all research-oriented faculty) and concerns by junior faculty about balancing their efforts in research, education, and patient care provided the impetus to create the Pediatrics Research Office.

The current goals of the Research Office are to:

- provide up-to-date information on federal and nonfederal funding sources for faculty depending on their professional and research interests,
- consult on developing laboratory procedures for basic and clinical science research,
- consult on research design, methodology, and analysis and conduct power analyses,
- consult on computer use and communication (e.g., INTERNET), designing and developing data collection, protocols, and computerized research databases,
- conduct biostatistical, and other types of analyses (e.g., Fourier analysis, numerical taxonomy), and generate computer graphics of scientific data,
- develop idiosyncratic software (FORTRAN and BASIC) for data manipulation or analysis (e.g., selective analysis of components of DNA molecules for generating phylogenetic trees),
- identify medical and graduate students in the College of Medicine and graduate and undergraduate students in the Colleges of Allied Health, Nursing, and Arts & Sciences who might be interested in working with Pediatrics faculty on research projects,
- identify intramural and extramural professional and academic colleagues as potential collaborators with Pediatrics faculty on research projects,
- help develop materials to be used in writing papers and research proposals (e.g. compilation of NIH faculty biosketches, provision of "boilerplate" for NIH proposals), and
- help develop publication-quality figures for poster presentation and publication.

With limited funds for pilot projects and increasing faculty clinical work loads, one real concern in promoting faculty research activities has been finding students interested in working with faculty in collecting and analyzing data. Over the last several years, Pediatrics faculty have been successful in involving students from the Summer Medical Student Research Program to help conduct their research. From these studies more than two-dozen presentations with published abstracts have resulted and a number of manuscripts are being prepared for publication. To expand these activities, students outside of the College of Medicine have been encouraged to become involved in faculty projects. For example, over the last five years, four students from Sociology & Anthropology have worked with Pediatrics faculty. Several research presentations at professional

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meetings, four published papers, and a M.A. thesis in Sociology have resulted from these activities. More recently, one student from Allied Health (Speech Pathology & Audiology Program) and one from Nursing (Nurse Practitioner Program) have worked on separate projects with Drs. Trimm, Hackman, and Hoff. One published paper and a submitted paper have resulted. In addition, we are currently establishing a relationship with the Physician's Assistants Studies (PAS) Program and we anticipate having PAS student research assistants working on future clinical research projects with faculty year-round.

The stated mission of the Pediatric Research Office is to encourage research and publishing, especially by junior faculty. In this it is beginning to see some success. In addition, another of its goals is to help obtain extramural funding for pediatric research. At the moment, one proposal for a "young physician-scientist" award has been submitted to NIH and another is anticipated. Also, two junior faculty have obtained a grant as part of a multicenter clinical trial on the use of a monoclonal antibody against severe pediatric RSV infection. It is anticipated that the activities of the Pediatric Research Office will "bear fruit" as more faculty are successful in obtaining extramural support for research and in developing their careers in academic medicine.

MEDICAID WAIVER GRANTED

Secretary of Health and Human Services Donna Shalala announced on December 6 that the city of Mobile, Alabama, and the surrounding area had been granted a section 1115 research and demonstration waiver. Under the program, which will last five years, the delivery of health care services to the Medicaid population will be coordinated by the BAY Health Plan. Contracting providers include the University of South Alabama Hospitals, affiliated outpatient centers, the College of Medicine, USA Physicians and Clinics, and Federally Qualified Health Centers such as the Mostellar and Franklin Clinics.

The BAY Health Plan will begin provider and beneficiary education on January 1, 1997 and begin enrolling beneficiaries on April 1, 1997. The initial enrollment group will consist of 32,000 Medicaid beneficiaries.

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

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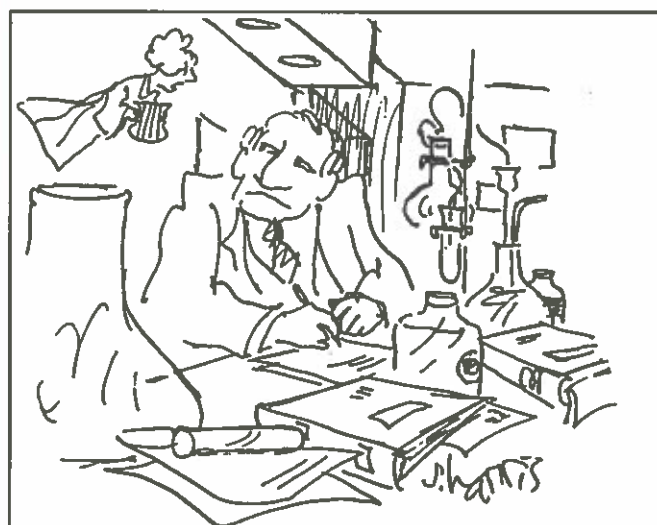
BASIC MEDICAL SCIENCE GRADUATE RESEARCH FORUM/ VISITATION DAY

The Basic Medical Sciences (BMS) Ph.D. Graduate Program in the College of Medicine will host its third Research Forum/Visitation Day on Friday, January 24, 1997, in the Medical Sciences Building Auditorium. The program is being held to promote the research being conducted by graduate students, faculty, and fellows within the five major departments that constitute the BMS Graduate Program. The forum is also intended to encourage the interest of undergraduate students in the Basic Medical Sciences Graduate Program.

The day's events will begin with a welcome by Dr. Samuel Strada, Senior Associate Dean for the College of Medicine, to the visiting undergraduate students from colleges across the Southeastern region of the country, including USA students. Dr. Mark Gillespie, Director of Graduate Studies for Basic Medical Sciences, will introduce the Graduate Program and the Basic Medical Sciences Department Chairs, prior to the individual departmental discussions and presentations. These presentations will allow the visiting students an opportunity to gain general information about the Graduate Program and more specific information about departmental requirements for admission and completion of the Ph.D. degree in Basic Medical Sciences.

Visiting students, BMS Graduate and College of Medicine Faculty, BMS Graduate Students, and other distinguished guests will have the opportunity to view and discuss research forum poster presentations, tour research labs, and attend disease-related research slide presentations prior to lunch.

The day's program will conclude with a lecture by Dr. Steven Goodman, Director of the USA Comprehensive Sickle Cell Center, who will give a summary of the research being conducted at the center.



*"I can only help you with tiny, little steps. As for
breakthroughs, you're on your own."*

AWARDS...

Dr. Robert N. Lausch, *Professor of Microbiology and Immunology*, has received a research grant of \$847,247. The 5 year grant is awarded by the National Eye Institute, a division of the National Institutes of Health, and will support research directed toward gaining new information on how to control ocular inflammation. Inflammatory responses are a common clinical problem that may involve any part of the eye. Dr. Lausch's research will focus primarily on inflammation that occurs in the cornea following infection by agents such as herpes viruses. Infections by these viruses can induce severe inflammation which in turn can lead to corneal scarring and permanent visual impairment. Consequently, the National Eye Institute has targeted this area as one in which additional research is urgently needed. The research will concentrate on cytokines which are cellular messengers that play a critical role in inducing and regulating inflammation. The principal agent to be studied is interleukin 10, a natural occurring cytokine which has anti-inflammatory properties.

Dr. John E. Oakes, a *Professor in the Department of Microbiology and Immunology*, and an authority on the molecular biology of herpes viruses will assist in the research. Both Lausch and Oakes hold joint appointments in the Department of Ophthalmology, and are members of the Lions/Research Institute. The researchers said that they expect the information gained from their forthcoming experiments will provide new insights into ways to minimize corneal inflammation without impairing the host's capacity to eradicate the virus from the eye.

Christopher Sneckenberger, a third year medical student, was presented the annual Ciba-Geigy Award for Outstanding Community Service. He was recognized for his volunteer service to St. Mary's Home and the Adult Literacy Program in Mobile through Sigma Chi, his fraternity at USA, and to his hometown Boy Scout Troop in Enterprise, AL.

NATIONAL PRIMARY CARE DAY:

Student Leadership Providing Momentum

More medical students are joining a growing, national trend and choosing to become primary care physicians. How long will this trend last and will it sufficiently meet America's need for primary care physicians? The third annual National Primary Care Day was held on October 10, 1996 — an event organized by medical students designed to keep the impetus on this trend. Student leaders took an afternoon off from lectures and rounds for the purpose of educating their peers about the rewards and challenges of primary care specialties.

Primary Care Day, coupled with the increasing educational emphasis on primary care within medical schools, appears to be having an impact. In 1995 twenty-eight percent of U.S. medical seniors indicated that they planned to pursue careers in primary care. The national percentage for 1996 is unavailable, however, seventy three percent of the USACOM graduating Class of 1996 selected residencies in primary care disciplines.

The student coordinator this year was senior student Neil Treece, who was assisted by a panel of senior and junior medical students. The USA student group hosted an afternoon seminar session with featured speaker Robert Gilliam, M.D., a family practitioner. Other guest speakers, including a panel of USAMC residents, participated in the program sharing their perceptions of a primary care residency and career pathways available in the generalist disciplines.

ADVANCEMENTS IN THE TREATMENT OF STROKE

With publication of the National Institutes of Health Tissue Plasminogen Activator (t-PA) Stroke Study results in the New England Journal of Medicine on December 14, 1995, t-PA became the first therapy of proven benefit for patients with acute ischemic stroke. The trial found that carefully selected stroke patients who received t-PA treatment within 3 hours of their initial stroke symptoms were at least 30% more likely than untreated patients to recover from their stroke with little or not disability after three months. **Dr. John Rothrock**, Professor and Chair of Neurology, and **Dr. Richard Zweifler**, Assistant Professor and director of the USA stroke team, were investigators in the study while at the University of California- San Diego. The stroke center has been administering t-PA to all eligible patients at USA Hospitals since mid January 1996. Until now, acute stroke has been a condition that, once it occurred, was untreatable, said Zweifler.

Unfortunately, the data indicate that only about 1/3 of all ischemic stroke patients present to USAMC or USA Knollwood Park Hospital within 3 hours of symptom onset. In an attempt to increase the percentage of stroke patients presenting to the hospital within 3 hours and, therefore, being potentially eligible for treatment with t-PA, the stroke center has implemented an intensive public and professional education program, said Zweifler. This program has focused on educating the lay public regarding the signs and symptoms of stroke and encouraging the use of 911 calls. The stroke team has also implemented a 24 hour/day, 7day/week "stroke code" system at USA Hospitals, designed to reduce in-hospital delays in the evaluation and treatment of stroke patients. As this is a novel approach to stroke management in the south alabama region, extensive physician education has been necessary to insure awareness of the program, explained Zweifler.

More information on t-PA and its use for stroke treatment can be obtained through the USA neurology clinic at (334)460-7009.

The National Institutes of Health

and the

Cardiology Division

of the

University of South Alabama

are conducting

A study of the impact aspirin can have on the prevention of strokes in patients with atrial fibrillation. Patients are needed with atrial fibrillation, no history of stroke, and normal or well-controlled blood pressure. If you fit the above-mentioned traits and are interested in taking part in this study, please call Carolyn Hupp at 334-471-7919.

Cardiology Division
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