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The Beat



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APRIL 1997

NOVEL TREATMENT STRATEGIES FOR SICKLE CELL DISEASE

Research in the laboratory of DR. BETTY PACE focuses on the molecular control of globin gene expression. The primary goal is to develop new treatment strategies for patients with Sickle Cell Disease (SCD), an inherited hemoglobinopathy disorder which affects over 60,000 African-Americans. Eight percent of African-Americans are heterozygous carriers of the sickle gene and are said to have sickle cell trait. The abnormality in sickle cell disease involves a single point mutation in the β -globin gene which leads to a substitution of the amino acid valine for glutamic acid. The single base change results in polymerization of hemoglobin S and the sickled shape of the red blood cell. The clinical manifestations of sickle hemoglobinopathies are linked directly or indirectly to the propensity of deoxygenated hemoglobin S to polymerize. The symptoms in sickle cell disease are related to the chronic hemolytic anemia and the tissue ischemia caused by vaso-occlusion. Recurrent ischemic pain, particularly abdominal and musculoskeletal pain, occur throughout life. Complications of SCD include splenic dysfunction, which can lead to an increased risk of overwhelming infection with encapsulated bacteria, especially pneumococci and the acute chest syndrome characterized by fever, chest pain and acute pulmonary infiltrate with hypoxia. The latter complication is now a leading cause of morbidity and mortality in older patients. In addition, strokes occur in one out of ten children and gallstones are common in adolescence. Recurrent episodes of vaso-occlusion and tissue ischemia cause a myriad of acute and chronic problems in several organ systems.

Although the molecular defect leading to SCD has been known for many years, few advances have been made in the treatment strategies of patients with sickle cell disease. Given the number of patients affected by this disorder and the magnitude of the healthcare problems associated with SCD there is an ongoing need for researchers in this field.

In 1981, after Dr. Pace received her M.D. degree with honors from the Medical College of Wisconsin in Milwaukee, Wisconsin, she began her journey to become a basic science researcher in the field of the transcriptional regulation of globin gene expression. Dr. Pace finished her pediatric residency training at the Medical College of Wisconsin and shortly thereafter joined the full time faculty as an

Assistant Professor and the Medical Director of the Comprehensive Sickle Cell Program. Under her leadership the Sickle Cell Program secured state funding and the neonatal screening program for sickle cell disease was established for the entire state of Wisconsin. In addition, the Wisconsin center participated in the Prophylactic Penicillin Study (PROPS I) in 1984 which formed the basis for the current recommendation that all infants with sickle cell disease receive penicillin starting at three months of age. Dr. Pace was also a participant in the National Institutes of Health Consensus Conference to establish a basis for newborn screening for sickle hemoglobinopathies across the nation.

Not satisfied with a successful career in clinical medicine, Dr. Pace added a second dimension to her career and entered a fellowship training program in hematology/oncology at the University of Colorado Health Sciences Center in 1987. She studied molecular biology in the laboratory of Dr. William Seltzer, a medical geneticist. They studied the mutations present in the globin promoter region in sickle cell patients with persistent elevations of fetal hemoglobin. This work led to the identification of novel mutations. Now dedicated to a career in basic research, Dr. Pace accepted a post-doctoral fellowship at the University of Washington in the Department of Medical Genetics. She trained in the laboratory of Dr. George Stamatoyannopoulos, a world leader in hemoglobin research. Dr. Pace began research which combined her previous clinical expertise and basic research skills to establish, in collaboration with her colleagues, a transgenic mouse model to screen and identify new agents to induce fetal hemoglobin production. Fetal hemoglobin (a product resulting from activation of γ -globin gene expression) can effectively block polymerization of sickle hemoglobin and improve symptoms in sickle cell patients. Several transgenic mouse lines with various fragments of the human β -globin locus were established and tested. Using these transgenic mice Dr. Pace was the first researcher to establish an *in vivo* model system for screening fetal hemoglobin-inducing agents. Her studies focused on agents such as butyric acid, erythropoietin, hydroxyurea and several other fatty acid compounds. Using the transgenic mouse model Dr. Pace and her colleagues

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quickly learned that the short chain fatty acids, propionic acid, valproic acid and acetate could be used as fetal hemoglobin-inducing agents which could be potentially useful to treat sickle cell patients. As a direct result of these studies valproic acid is presently being evaluated in clinical trials.

In 1994, Dr. Pace was recruited to the University of South Alabama Comprehensive Sickle Cell Center as an Assistant Professor in the Departments of Pediatrics and Structural and Cellular Biology. She is continuing her basic research in the field of molecular mechanisms for globin gene expression with particular emphasis on the agents butyric acid and hydroxyurea. Her research efforts have lead to the first identification of a potential butyrate response element (a DNA sequence necessary for induction of γ gene expression by butyrate) in the γ -globin gene promoter. Similar response elements have been identified in the promoters of the long terminal repeat of the HIV virus, the histone H1 gene and the T lymphocyte CCP1 gene. Dr. Pace and her colleagues have continued work in this area through funding from the Alabama Affiliate of the American Heart Association. Last year Dr. Pace was awarded a Career Development Award from NIH to continue her effort to unravel the molecular mechanism for γ gene reactivation by butyrate and to identify the nuclear *trans*-acting factors that control the process. A second approach taken by Dr. Pace's laboratory to increase γ gene expression is to γ inhibit gene silencing during normal hematopoiesis. The Pace laboratory has begun some very exciting work to examine the role of Interleukin-6 in γ -globin gene silencing during normal hematopoietic development. They have demonstrated a down regulation of the fetal hemoglobin gene by Interleukin-6, a finding which may have great implication for the development of new therapeutic strategies. This work was initiated by Dr. Pace in collaboration with Dr. Surendra Baliga (*Dept. of Pediatrics*) and Mr. Carlos Monterio, (*Dept. of Structural and Cellular Biology*). Much of the data was obtained by Ms. Amy Ferry a graduate student in Dr. Pace's laboratory as part of her Ph.D. dissertation project. Ms. Ferry is also analyzing the potential *trans*-acting factors that are involved in β -globin gene activation following γ -gene silencing during normal hematopoietic development. In parallel studies, Dr. Lei Xu, a M.Sc. student in Biology will be using antisense oligodeoxynucleotide technology to inhibit the β -globin gene directly in an effort to reactivate the fetal hemoglobin



gene. Collectively, these efforts will help to identify potential new treatment strategies for sickle cell patients.

Dr. Pace continues her clinical duties in the Division of Pediatric Hematology/Oncology headed by Dr. Y. Yang where she serves as the Director of Outpatient Sickle Cell Services. Dr. Pace is able to skillfully integrate her basic science expertise into the clinical realm through a collaboration with Dr. Susan Perrine (*Boston University*), known nationally for her Phase II clinical trial using arginine butyrate acid to induce fetal hemoglobin in sickle cell patients. Long term Dr. Pace states "I would like to establish a teaching laboratory focused on different mechanisms for globin gene regulation which can be applied in a clinical setting to improve the symptoms and quality of life for sickle cell patients."

CONGRATULATIONS.....

William A. Gardner Jr., M.D., Associate Dean for Clinical Affairs, and Louise L. Locke Distinguished Professor and Chair of the Department of Pathology, has been appointed Chair of the Scientific Advisory Board of the Armed Forces Institute of Pathology (AFIP).

Dr. Gardner was appointed to the AFIP Board by the U.S. Secretary of Defense and was selected from the civilian community based on his national, and international prominence in medicine and science. He serves the public interest as an advisory board member to the Director of the AFIP, providing professional advice and guidance in matters related to programs, policies and procedures of the Central Laboratory of Pathology for the Department of Defense and other federal agencies.



Amjad Hossain, Ph.D., *Assistant Professor of Obstetrics and Gynecology*, and co-authors, Botros Rizk, M.D., Ian Thorneycroft, Ph.D., M.D. (*OB/GYN*) and Salien Barik, Ph.D. (*Biochemistry and Molecular Biology*), were presented the Serono Scientific Award for the best published paper of the year in the Middle East Fertility Society Journal. The paper entitled "A microscopic approach of sperm preparation for intracytoplasmic sperm injection" was given special recognition by Serono Pharma Internacional, a nonprofit organization that supports reproductive biology research. The authors of "the paper of the year" were awarded a plaque and a check for \$2,500. The manuscript was the outcome of the intramural grant awarded by the USA College of Medicine to Dr. Amjad Hossain.



The Laboratory at the University of South Alabama Doctors Hospital received full Accreditation by the College of American

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Pathologists (CAP), based on the results of a comprehensive on-site inspection.

The laboratory was advised of this national recognition and were congratulated for the "Excellence of the services being provided." The laboratory at USA Doctors Hospital is one of more than 5,000 accredited laboratories nationwide.

The College of American Pathologists is a medical society serving more than 14,500 physician members and the laboratory community throughout the world. It is the world's largest association composed exclusively of Pathologists and is widely considered the leader in laboratory quality assurance. The CAP is an advocate for high-quality and cost-effective medical care.



Five residents the University of South Alabama's Department of Pathology were chosen to present abstracts at a recent Southern Medical Association meeting. Only 15 pathology residents were selected for the honor. The five were Drs. Norman Bell, Peter Bozner, Allison Graves, Tommy Yates and Dawn Dye.

Also, Dr. Maggi O'Brien's abstract was selected for presentation at a seminar on gynecologic pathology. Dr. Judy King, a fellow in anatomic pathology, was elected chair of the association's pathology section.



Maria Soto-Aguilar, M.D., assistant professor of medicine and pediatrics, has been appointed to the editorial board of the *Annals of Allergy and Immunology*, a leading clinical journal in the immunology field.



Mary C. Tyrell, M.D., assistant professor of radiology, won the "Excellence in Design" award for a poster presentation titled "Paraduodenal Hernias," at the 1996 Radiological Society of North America Annual Meeting.



Richard D. deShazo, M.D., professor of medicine and pediatrics and chair of the Department of Medicine, was elected secretary of the American Board of Allergy and Immunology in Philadelphia.

The board is responsible for the development and administration of national examinations leading to certification in the adult and pediatric subspecialties of allergy and clinical immunology.

RESEARCHERS AGREEING ON PROCESS OF RESEARCHING SCIENCE AND RELIGION

Unique-day conference addresses influence of genetics on spirituality, links between religion and health, youth crime and addiction.

Frank deGruy, M.D., Professor and Chair of the Department of Family Practice and Community Medicine, attended a conference in Miami, Florida exploring the role of spirituality in medicine. According to Dr. deGruy, "the impact of spirituality on the health of our patients is an incredibly fruitful area of study and participating in this conference has given me an excellent opportunity to work with researchers from across the country who are also looking at this variable."

Researchers at the conference are starting to agree on the basic processes for researching spirituality and health. David B. Larson, president of the National Institute for Healthcare Research announced at the final session. The conference drew more than 70 of the nation's leading health care researchers and medical practitioners who convened for the second in a series of three conferences to formalize the study of spirituality and health and the incorporation of this topic into mainstream medical research. The conference, entitled "Scientific Progress in Spiritual Research" was sponsored by the National Institute for Healthcare Research (NIHR) and the John Templeton Foundation. NIHR collects, reviews, and publishes research addressing understudied social and religious factors in physical and mental health.

According to Dr. Larson, the researchers agreed on ways that the scientific method can be used to study the impact of religion and spirituality on individuals' health and well-being. They also agreed that future programs and studies should focus on religion's role in intervention; its impact over time (longitudinal); training of researchers and investigators; and treatment mechanisms.

There was consensus among the conferees about the direction of spiritual research in a scientific setting. According to conference moderator Harold Pincus, M.D., Deputy Medical Director, American Psychiatric Association, "science and religion are no longer at war. The path at reconciliation may be blazed by the data."

Conference participants were divided into four groups: physical health, mental health, addiction disorders, and neuroscience. Researchers within each of these groups addressed how spirituality can be best measured and defined. They also focused on the available scientific data on whether religious interventions improve mental health care outcomes.

WELLCOME VISITING PROFESSOR IN BASIC SCIENCES

John V. Weil, M.D., a Professor of Medicine in the Division of Cardiology and Director of the Cardiovascular Pulmonary Research Laboratory at the University of Colorado Health Sciences Center, was selected as the 1997 Wellcome Visiting Professor in the Basic

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Medical Sciences. His visit to the USA College of Medicine was supported by the Burroughs Wellcome Fund and awarded by the Federation of American Societies for Experimental Biology. The purpose of this award is to encourage interdisciplinary exchange of scientific information.

During his visit, Dr. Weil met with members of the local pulmonary and Sickle Cell research communities. In particular, a multi-departmental group (pathology, physiology, and pharmacology) is planning to submit a program project grant for which Dr. Weil served as a consultant. Dr. Weil also presented a Distinguished Scientist Seminar Lecture on March 6, entitled "Pulmonary Vascular Injury in Sickle Cell Disease", sponsored by the Department of Pharmacology.

Among his scientific accomplishments, Dr. Weil established that hypoxic ventilatory responses display considerable inter-individual variability suggesting a genetic link to oxygen sensing. He has participated on many national review boards, and is currently a member of the Parent Review Committee at NIH for evaluating program project grants. His current research interests focus on the impact of sickle cell disease in lung vascular dysfunction.

GLUSMAN HONORED FOR OUTSTANDING LEADERSHIP



Brenda Glusman, Health Education Specialist for USA Student Health Services, Department of Medicine, was nominated by the Mobile County HIV Prevention Planning Group for the Robert Wood Johnson Community Health Leadership Award. Glusman's role as Health Education Specialist is to develop, implement, direct and evaluate health education programs for USA students and

the wider university community.

The Robert Wood Johnson Community Health Leadership Program each year honors ten outstanding and largely unrecognized leaders in the field of community health who have created or significantly improved programs that further develop key health services within their communities. Recipients represent a wide range of creative builders within their organizations. They are people who neither expect nor look for glory—but they do have dreams for their programs.

Brenda Glusman's hard work and dedication include prevention outreach programs designed to target young adults and health issues significant to this population such as substance abuse, teen pregnancy, STD's, and HIV/AIDS. In order to enhance education of these topics, she developed a peer education program in 1993 to tackle these issues. This program is designed to encourage students to expand community outreach in order to provide middle and high school youth the educational training opportunities to become certified peer educators in their schools and to accept responsibility

for their own health and well being. Programs are developed for and taught by trained peer educators with the objective of providing their peers with factual health information and resources, develop self esteem, behavioral and negotiation skills, and provide positive peer role models. "USA is in the prime position to provide the community and surrounding service areas with effective health prevention programs and outreach," said Glusman.

Other accomplishments which have placed a positive impact on the adolescent community's health prevention education efforts include the implementation of the first peer education program, the first structured training program for at risk African-American youth as well as teens at large, and the development of a statewide HIV Teen Symposium developed in 1995. Through her success and efforts, adolescents in our community and state are becoming better informed and educated to deal with the social and health issues they encounter on a daily basis.

Glusman is a member of the Mobile AIDS Coalition, Mobile County HIV Prevention Planning Committee, Mobile County HIV Care Consortium, Mobile Aids Support Services, Provider Council for Child and Family Services, and the Alabama Department of Public Health.

For more information on these educational programs please contact:

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**** NEWCOMERS ****



Ashmead Ali, M.D., *Assistant Professor of Pediatrics*, received a M.B.B.S. from the University of West Indies. He completed an obstetrics residency and a neonatology residency at Mt. Hope Women's Hospital in Trinidad. Dr. Ali completed his pediatric residency at the University of Texas and additional fellowship training in neonatology at the University of Miami/Jackson Memorial Hospital.



Dirk M. Dhossche, M.D., *Assistant Professor of Psychiatry*, received an M.D. degree from the State University of Gent, Belgium. He completed his psychiatric residency at State University of New York at Stony Brook. He also completed a clinical research fellowship at State University of Limbury, The Netherlands, and a child psychiatric fellowship at Sophia Children's Hospital, The Netherlands.



Stefan Ichim, M.D., *Assistant Professor of Anesthesiology*, received a M.D. degree from the School of Medicine, Burcharest, Romania. He completed an internship in medicine and a anesthesiology residency at the University of Washington.



Jack W. Olson, Ph.D., *Professor of Pharmacology*, received a B.S. in pharmacy from the University of New Mexico and a Ph.D. degree in pharmacology from the University of Southern California. He completed a National Cancer Institute postdoctoral research fellowship in the department of pharmacology at the University of Arizona and was previously on the faculty at the University of Kentucky.



Miguel A. Pappolla, M.D., *Associate Professor of Pathology*, received an M.D. degree from the University of Buenos Aires, Argentina. He completed his residency in pathology at Northeastern Ohio Universities, College of Medicine-Affiliated Hospitals and a neuropathology fellowship at Case Western Reserve University and the Cleveland Clinic Foundation. He was previously on the

faculty at the University of Texas Medical School at Houston.

**RENOWNED RESEARCHER
DELIVERS FRAZER LECTURE**

Moses Judah Folkman, M.D., a Senior Associate in Surgery and Director of the Surgical Research Laboratory at Children's Hospital in Boston, delivered the fourteenth annual Emmett B. Frazer Endowed Lecture on March 14 at the University of South Alabama Medical Center.

"We are privileged to have Dr. Folkman speak in Mobile," said Dr. Randall Powell, chief of the USA Division of Pediatric Surgery. "His work as a researcher, clinician and scientist is recognized around the world."

Dr. Folkman received his medical degree from Harvard Medical School, graduating with magna cum laude distinction. As a student at Harvard, Folkman worked in Dr. Robert Gross' laboratory and developed the first atrio-ventricular implantable pacemaker. For this work, he received the Boyston Medical Prize, the Soma Weiss Award, and the Borden Undergraduate Award in Medicine.

Dr. Folkman has received many awards and honors from prestigious national and international organizations. He received a 10-year MERIT award in 1989 from the National Cancer Institute. He was elected to the National Academy of Sciences and the Institute of Medicine in 1990 in recognition of his pioneering research on angiogenesis. He also received the Gairdner Foundation International Award from Canada in 1991.

The Emmett B. Frazer Lectureship was established in 1982 at USA's College of Medicine for the purpose of giving local surgeons the opportunity to discuss current practices with surgical leaders from around the country.

Dr. Frazer, who died in 1985, was a Mobile physician for more than 60 years and was internationally recognized for his accomplishments as a surgeon. He was a pioneer in surgical practices and the first surgeon with specialized training in the surgical sciences to practice in Mobile.

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

Karrye E. Jackson
University of South Alabama
College of Medicine
CSAB 170
or
FAX (334) 460-6073

"MATCH DAY" RESULTS

For the fifth consecutive year, more than half of graduating USA seniors will pursue training in primary care for at least their first year of residency. The data are provided by the National Residency Matching Program (NRMP), the primary route by which applicants to residency programs obtain training positions at U.S. teaching hospitals. Sixty-six percent, or 43 USA graduating seniors selected a residency in primary care, reflecting a national trend toward generalist specialties, defined as internal medicine, family practice and pediatrics. Last year, 73% of USA seniors matched to these specialties. Overall, the rate of USA medical school graduates entering primary care areas has continued to rise since 1991.

The NRMP national data indicate that a total of 13,554 first-year residency positions were matched by U.S. seniors. Since 1952, the NRMP has served as an important indicator of the career interests of U.S. medical school graduate and other physicians who pursue training in U.S. residency programs.

Seniors waited anxiously to hear about their residency positions on Wednesday, March 19, 1997. The results of "Match Day" were distributed at 11:00 am during a reception held at the USA Brookley Conference Center. A total of 67% of USA graduating seniors successfully matched to their first choice of residency programs.

— RESIDENCIES RECEIVED BY DISCIPLINE —

	Class of 1993		Class of 1994		Class of 1995		Class of 1996		Class of 1997	
PRIMARY CARE:	37	56%	40	58%	36	60%	47	73%	43	66%
Internal Medicine	17	26%	18	26%	14	23%	26	41%	12	18%
Family Medicine	10	15%	12	17%	16	27%	15	23%	23	35%
Pediatrics	9	14%	7	10%	5	8%	4	6%	7	11%
Med/Peds	1	2%	3	4%	1	2%	2	3%	1	2%
Anesthesiology	3		7		3		2		3	
Emergency Medicine	0		1		1		2		2	
Neurology	3		2		1		0		0	
Neurological Surgery	0		0		2		0		0	
Ob/Gyn	3		3		2		4		5	
Ophthalmology	0		2		2		1		1	
Orthopedics	4		0		1		0		0	
Otolaryngology (ENT)	0		1		0		0		1	
Pathology	2		4		4		2		4	
Psychiatry	1		2		1		4		0	
Radiology	2		0		2		2		1	
Surgery	10		7		2		0		4	
Transitional	0		0		2		0		0	
Urology	0		0		1		0		1	

CLIKAS HONORED FOR PLANTING OF "THE TREES OF HIPPOCRATES"

A reception was held on March 9, 1997 at the USA College of Medicine, Medical Sciences Building, commemorating The Trees of Hippocrates donated by the Clikas family. The trees are offshoots of the Tree of Cos in Greece, under which the "Father of Medicine" studied. The trees were acquired as a gift from Schering laboratories by the family of Steve and Sophia Clikas. Mrs. Clikas was honored by the International Hippocratic Foundation of Cos in Greece for the trees she secured and had planted at USA. Mrs. Clikas' diligence was the result of her desire to bring honor and recognition to the university and to Mobile.

The University of South Alabama is the only college in the world to have two trees of Hippocrates planted at either side of its doors from the seedling of the mother tree, THE TREE OF HIPPOCRATES. USA unveiled a plaque commemorating the planting of the trees and a reception honoring Mrs. Clikas.



Mrs. Sophia Clikas and Clyde (Sid) Huggins, Ph.D., Emeritus Faculty, Department of Biochemistry, stand under one of two Trees of Hippocrates they planted in 1975. Mrs. Clikas holds a photograph showing herself, her late husband and Dr. Huggins with one of the seedlings.

FORMER USA PROFESSOR ALDEN DUDLEY, M.D. PRESENTS TOREN LECTURE

Alden W. Dudley, Jr., M.D. visited the University of South Alabama as the Toren Lecturer in February hosted by the Department of Pathology. The annual Toren Lectureship honors the memory of the late Dr. E. Clifford Toren, a founding faculty member of the Department of Pathology.

Dr. Dudley is currently chief of Pathology and Laboratory Medicine Services at the Veterans Administration, New Jersey Health Care Systems, having assumed this position in the Fall of 1996. His former appointments include Professorships of Pathology at Baylor College of Medicine in Houston, Medical College of Ohio, and as Professor and Chair of the Department of Pathology at University of South Alabama.

Dr. Dudley delivered lectures to the Sophomore Pathology and Laboratory Medicine students on muscular, neuromuscular, and demyelinating diseases and toxins and reviewed neuropathology cases with Pathology and Neurology Housestaff. In addition, he presented the Distinguished Scientists Seminar on "Survival Technics in Academic Medicine: Education, Patient Care, and Research."

Perhaps more people would take interest in medical research if only they understood the practicing physician's relationship to research, and every person's own likely dependence on medical research for health and even for life itself.—Ben May, 1952

Mobile Philanthropist

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