

2005/2006 ANNUAL REPORT



SAFAR CENTER FOR RESUSCITATION RESEARCH



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MISSION STATEMENT

The mission of the Safar Center for Resuscitation Research is to identify and promote ever-improving methods of preventing premature death and reducing associated disability from trauma and cardiac arrest in people with “hearts and brains too good to die.”

The Safar Center for Resuscitation Research at the University of Pittsburgh School of Medicine was founded by the late Dr. Peter Safar in 1979, initially as the International Resuscitation Research Center. In recognition of Dr. Safar’s innumerable contributions to the field of resuscitation medicine, it was renamed the Safar Center for Resuscitation Research in 1994. The Safar Center’s current research programs include Traumatic Brain Injury, Child Abuse, Cardiac Arrest, Emergency Preservation and Resuscitation, Hemorrhagic Shock, Combat Casualty Care, and Rehabilitation of CNS Injury. Center investigators work closely with the clinical depts. of Critical Care Medicine, Surgery, Neurological Surgery, Anesthesiology, Emergency Medicine, and Physical Medicine and Rehabilitation at both the University of Pittsburgh Medical Center and Children’s Hospital of Pittsburgh. In addition to conducting basic research, the Safar Center also provides training to the next generation of resuscitation researchers. The Center is a 20,000 square-foot freestanding research facility that houses the laboratories of scientists and clinician-scientists working across a broad spectrum of fields important to resuscitation medicine.

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Featured on the cover: Historical display depicting the Peter Safar story that is located in the newly dedicated conference room of the Safar Center for Resuscitation Research.

LETTER FROM THE DIRECTOR...



Our investigators are working in a number of important areas of research relevant to resuscitation medicine, including traumatic brain injury, child abuse, cardiac arrest, emergency preservation, hemorrhagic shock, combat casualty care, and rehabilitation. Our research spans the gamut from the field to rehabilitation. We are also a unique site for training of future clinicians and scientists interested in a career in pediatric neurointensive care and resuscitation-related research.

This was a special year at the Safar Center for Resuscitation Research. On June 27, 2006 we held the dedication of the new Safar Conference room in our Center. The new conference room contains an impressive historical display that I believe effectively captures the remarkable life of the late resuscitation pioneer Dr. Peter Safar. A portion of that display is shown on the cover of this report. In addition to the series of historical panels that outline the “Peter Safar Story,” the display features a large display case that houses

On June 27, 2006,
we dedicated the new Safar
Conference Room in the
Safar Center which features
an outstanding historic
display on the remarkable
career of the late Dr. Peter
Safar.

Mrs. Eva Safar gracing the Safar Conference Room dedication with her thoughtful commentary about Peter Safar and his ultimate dreams for the Safar Center.



a number of truly unique items such as the first “Resuscitate Anne” manikin, the collected publications of Peter Safar, and prototype airways that Dr. Safar used in experiments before the development of mouth-to-mouth resuscitation, among other items. In the conference room, one is also surrounded by a sampling of the myriad of prestigious honorary degrees and awards that Peter Safar received, along with an array of letters of commendation from distinguished individuals. The dedication included a ribbon cutting ceremony by Mrs. Eva Safar, historical opening comments by Senior Vice Chancellor of the University of Pittsburgh School of Medicine, Dr. Arthur Levine, a fascinating discussion by Mr. Tore Laerdal, CEO of Laerdal Medical, of the special friendship and catalytic interaction between the late Mr. Asmund Laerdal and Peter Safar, kind and encouraging remarks by Mrs. Eva Safar, and a dedication lecture on the

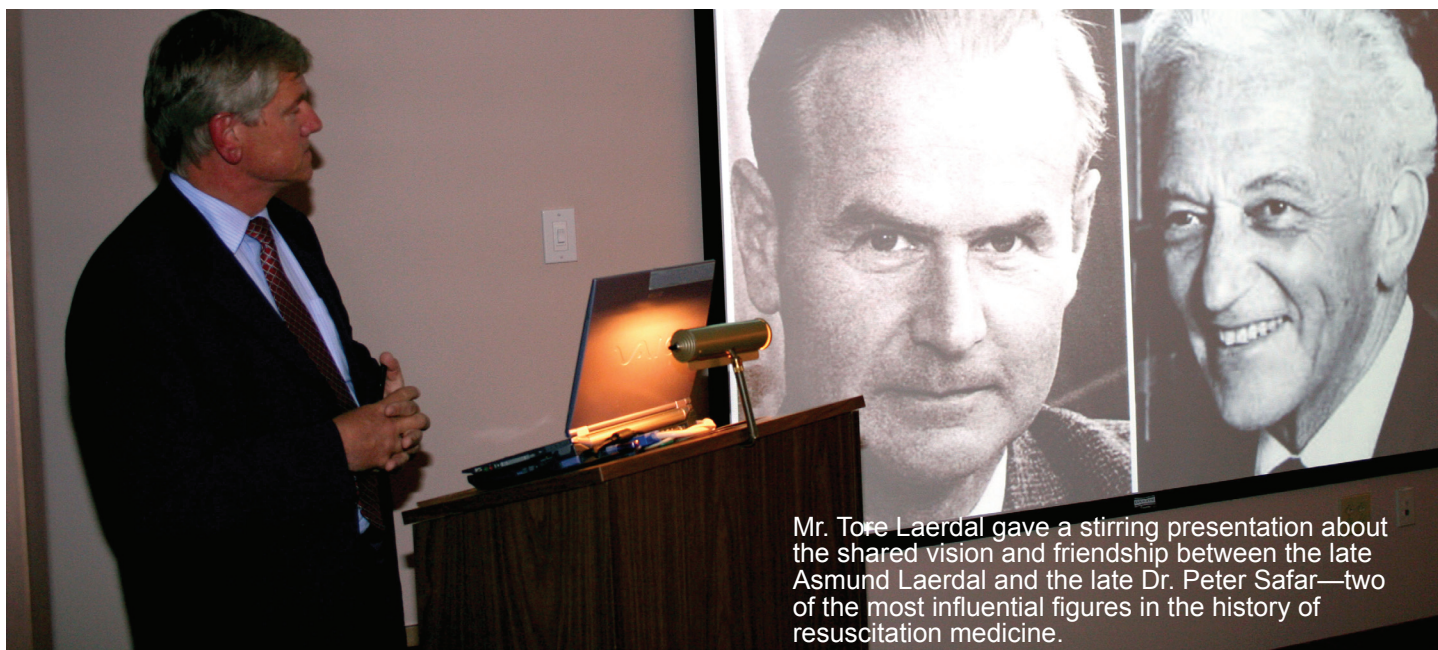
topic of “The Challenge of Clinical Trials in Traumatic Brain Injury” by our honored guest speaker, Dr. Ross Bullock, from the Department of Neurological Surgery at the Medical College of Virginia. Dr. Bullock’s life-long quest for the translation of novel therapies to the bedside in the field of severe traumatic brain injury and international reputation made him a perfect speaker for this event in Dr. Safar’s honor. A great time was had by everyone that attended and the new conference room generated accolades from every attendee. We owe a large debt of gratitude to Ms. Fran Mistrick, former secretary of Dr. Safar, for the incredible job that she did on the new conference room. I believe that it represents an enduring monument to one of the giants in the history of the University of Pittsburgh School of Medicine.



Senior Vice Chancellor Dr. Arthur Levine during his address at the dedication of the new Safar Conference Room.



From left to right: Dr. Ross Bullock, Mrs. Eva Safar, Dr. Patrick Kochanek, and Mr. Tore Laerdal at the Peter Safar Conference Room dedication.



Mr. Tore Laerdal gave a stirring presentation about the shared vision and friendship between the late Asmund Laerdal and the late Dr. Peter Safar—two of the most influential figures in the history of resuscitation medicine.

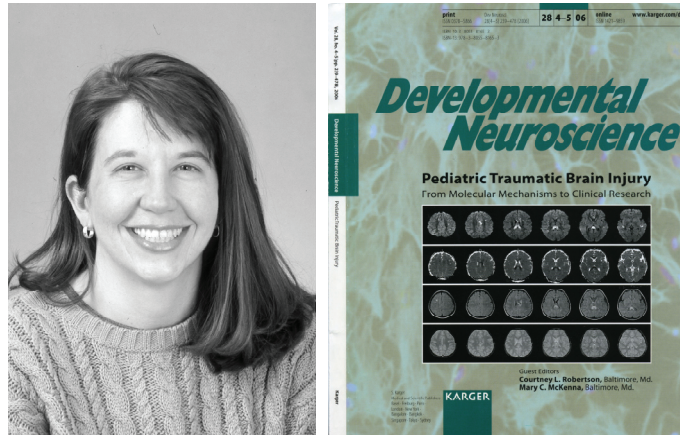
AWARDS AND ACCOMPLISHMENTS OF TRAINEES AND FACULTY

The most significant accomplishment at the Safar Center in the 2005-2006 academic year was related to the notoriety that our work on Emergency Preservation and Resuscitation (EPR) received in the lay press. Our work on EPR was featured in the December 2005 “Year in Ideas” issue of New York Times Magazine. Our EPR concept was selected as one of the top ideas world-wide in 2005. Congratulations to Drs. Samuel Tisherman, Xianren Wu, Wilhelm Behringer, Ala Nozari, Lyn Yaffe, Bob Wagner, and Mr. S. William Stezoski, COL Ronald Bellamy, and the many other individuals who have contributed so importantly to the evolution of this truly innovative project. In work related to that project, our group published two high impact papers this year in the prestigious journal *Circulation*.

Another terrific accomplishment in 2006 was the publication of a special issue of the journal *Developmental Neuroscience* devoted to the topic of traumatic brain injury in children.

NEW GRANTS

Although not reflected yet in the graphs of the 2005 funding that are depicted later in this report, as 2005 came to an end, Safar Center investigators put together a remarkable run of successes in the highly competitive funding arena. First, Dr. C. Edward Dixon was able to competitively renew the long-standing program project award in traumatic brain injury—namely, the University of Pittsburgh Brain Trauma Research Center. This 5 million dollar, 5-year award from the National Institute of Neurological Disorders and Stroke includes five bench-to-bedside projects by Drs. Robert Clark, Edward Dixon, Steven DeKosky, Steven Graham, and Patrick Kochanek in the field of traumatic brain injury. Congratulations to Dr. Dixon for allowing this prolific group to continue leading the way in experimental and clinical traumatic brain injury research. Dr. Kochanek was also fortunate to competitively renew funding by the National Institute of Child Health and Human Development of his T-32 program titled “Training in Pediatric Neurointensive Care and Resuscitation Research.” This has been an instrumental tool in training a number of highly successful clinician-scientists in the field of Pediatric Critical Care Research. Finally, as mentioned in the late-breaking news section of last year’s report, Dr. Kochanek was also funded as PI of a program project grant from the United States Army titled “Novel Nitroxide Resuscitation Strategies in Experimental Traumatic Brain Injury.” That 2 million dollar 4-year grant represents a collaboration between investigators at the Safar Center and Synzyme Technologies in Irvine, California—the manufacturers of novel resuscitation fluids under evaluation for a number of disease states. Among the other grants obtained by faculty and fellows this year, Dr. Hülya Bayır received a substantive salary stipend for her research from



That special issue was the brain child of Drs. Courtney Robertson and Mary McKenna at the University of Maryland. I am proud to say that Dr. Robertson is one of our highly successful former fellows.

the Laerdal Foundation. Hülya is an exceptionally talented young investigator in resuscitation medicine as reflected by her also receiving a scientist development award from the American Heart Association, National Affiliate. We thank the Laerdal Foundation for this generous support. These important new awards will be reflected in next year’s funding figures—and suggest a very bright future for research targeting brain injury and resuscitation at the Safar Center in 2007 and beyond. Finally, Dr. Ericka Fink was awarded a K-12 award from the National Institute of Child Health and Human Development to further her career development in the area of resuscitation research. Dr. Fink is a new faculty member at Children’s Hospital of Pittsburgh who recently graduated from our T-32 training program in Pediatric Neurointensive Care and Resuscitation Research.

We are also pleased to report on the development of a new funding pathway for trainees that was recently established by the Laerdal Foundation. The generous funding of fellow research at our center over the years by the Laerdal Foundation has been of great importance to our center and they have just established a new “Safar Fellowship” stipend to support young investigators in Scandinavian countries who are interested in carrying out research training related to the field of resuscitation at the Safar Center. This stipend also offers a parallel opportunity for trainees at the Winter Institute for Simulation Education and Research (WISER). Many thanks to the Laerdal Foundation for its continued support of our shared interest in developing young investigators who carry on the rich tradition of collaboration between Scandinavian and American investigators.

NEW ASSOCIATE DIRECTOR AND ASSOCIATE SCIENTISTS AT THE SAFAR CENTER

This year, Dr. Rachel Berger was invited to become one of the Associate Directors of the Safar Center, specifically of the research program focused on child abuse. Rachel is a superb young clinician scientist who has carried out some of the most important recent work in the field of inflicted childhood neurotrauma in the world—specifically, her work on the use of serum biomarkers to aid clinicians in making the difficult diagnosis of child abuse cases where brain injury is clinically silent. Rachel is clearly one of the top clinical investigators in our Center and a welcome addition to our Associate Directors. I am also pleased to welcome three new associate scientists to our Center, namely, Drs. T. Kevin Hitchens and James Menegazzi, and Lesley Foley, MS. Kevin and Lesley are scientists at the Pittsburgh NMR Center for Biomedical Research at Carnegie Mellon University who are important and innovative collaborators on the numerous projects at the Safar Center that are employing magnetic resonance imaging (MRI). The number of investigators and projects at the Safar Center involving MRI continues to expand—as a result of the superb collaborative efforts of Kevin and Lesley. I am

also pleased to welcome Dr. James Menegazzi as an associate scientist. Jim has an outstanding track record of nationally funded investigation in the area of cardiac resuscitation with a specific focus on the electrophysiology of ventricular fibrillation. I am confident that he will bring important expertise in this area to our Center and am extremely pleased that we will be able to work more closely with our colleagues in the Department of Emergency Medicine.

It is also noteworthy that Safar Center Associate Director Dr. Robert Clark assumed the role as Director of the Pediatric Critical Care Medicine (PCCM) fellowship training program at Children's Hospital of Pittsburgh. Bob has been the most prolific graduate of our training program. He is remarkably devoted to fellows in training—as reflected by the tremendous track record of accomplishments by the PCCM fellows that have trained in his laboratory. He is the perfect choice for this position.

SPECIAL EVENTS

In addition to the Dedication of the Safar Conference Room held on June 27, 2006, the 4th Safar Symposium and the 26th Peter and Eva Safar Annual Lectureship in Medical Sciences and Humanities were held on June 28th, 2006 at the University of Pittsburgh Biomedical Science Tower. Details of the Symposium and Lectureship are addressed later in this report. Finally, congratulations to S. William (Bill) Stezoski and Dr. Miroslav Klain on the occasion of their retirements. Bill's service to this Center and the University for over 50

years has been truly legendary and was detailed in last year's report. Similarly, Dr. Klain contributed to a number of projects over the years, particularly in his many collaborations with Dr. Safar. Most notable among these was his early work with high frequency ventilation, and his unique collaborative work with Drs. Peter Safar and Ernesto Pretto in the area of disaster reanimatology—studying the consequences and responses to a number of major earthquakes.

GUEST PROFESSORS

We were pleased to have four visiting professors this year at the Safar Center. In September 2005, Dr. Monica Vavilala, Associate Professor, Department of Anesthesiology, Pediatrics and Neurological Surgery, University of Washington, visited our Center and gave a lecture on "Rationale for Blood Pressure Management in Severe Pediatric Traumatic Brain Injury." Dr. Vavilala is a promising young investigator in the field of clinical pediatric traumatic brain injury research who is becoming one of the leading authorities on cerebral blood flow in children. We were also very pleased to welcome, in November 2005, Drs. Joseph B. Long and Richard Bauman, both of the Department of Polytrauma and Resuscitation Research, Division of Military Casualty Research at Walter Reed Army Institute of

Research. Their joint presentation addressed the important topic of "Far-forward Therapies for the Battlefield: Confronting the Needs of the Head-Injured Combat Casualty." This has led to an



Dr. Richard Bauman (left), Systems Integrator, Defense Research Projects Agency (DARPA); PREVENT (PREventing Violent Explosive Neurologic Trauma) and Dr. Joseph Long, Chief, Department of Polytrauma and Resuscitation Research, Division of Military Casualty Research at Walter Reed Army Institute of Research presented their new work on combined traumatic brain injury and hemorrhagic shock during their visit to the Safar Center. We have been fortunate to begin collaborations on the important topic of blast-induced TBI with Drs. Bauman and Long.

exciting new collaboration between our centers in the newly funded PREVENT BLAST initiative (see the "Late Breaking News" section of this letter). Our shared interest in polytrauma resuscitation made their presentation of special relevance to our investigative team. Finally, in May 2006, Visiting Professor Michael Dubick, PhD, Senior Research Pharmacologist, US Army Institute of Surgical Research, San Antonio, Texas gave a lecture on "Damage Control Resuscitation." Dr. Dubick's work is also highly germane to a number of ongoing projects at the Safar Center and his presentation was outstanding.

ACKNOWLEDGEMENT

I would like to thank everyone working at the Center for a terrific job this year. I am indebted to Linda Amick, Marci Provins, Fran Mistrick, Jackie Pantazes, and Julian Smith for their administrative and secretarial excellence. Marci also serves as my local editorial assistant for the journal *Pediatric Critical Care Medicine*. Special thanks are in order this year to Fran Mistrick, who did a truly spectacular job coordinating the production of the historical display in the new Safar Conference room in our Center. I also thank Mr. David Seaman of Signage and Graphic Identity at UPMC, and Mr. Dick White of RC White & Associates for production of the display and trophy cases. It is a special place for anyone that knew Dr. Safar, and has become a wonderful venue for conferences, journal clubs, and recruiting faculty, fellows, and residents. Fran also coordinates the annual Safar Symposium and Safar Lectureship. I also thank Henry Alexander, John Melick, Keri Feldman, Vincent Vagni, Xiecheng Ma, Dr. Lina Du, Paula Nathaniel, Ray Griffith, Jeremy Henchir, Sherman Culver, and Bill and Jason Stezoski for their contributions. I am amazed by the work ethic and commitment of everyone.

I thank Dr. Mitchell Fink and Ms. Susan Stokes for departmental support and Drs. Bayır, Berger, Callaway, Clark, Dixon, Jenkins, Kline, Tisherman, and Wagner for their assistance. The Associate Directors have made special contributions to our success. Thanks are also due to Drs. David Adelson, John Williams, Dade Lunsford, Ross Zafonte, Paul Paris, David Perlmutter, Hong Yan, Miro Klain, Steven Graham, Steven DeKosky, Glen Gobble, and Robert Hickey for their help. I am especially thankful to Dr. Ann Thompson for her continued support and guidance. I am also extremely grateful to Dr. Edwin Jackson at the Center for Clinical Pharmacology, Dr. Valerian Kagan at the University of Pittsburgh Center for Free Radical and Antioxidant Health, Drs. Chien Ho and Kevin Hitchens and Ms. Lesley Foley at the Pittsburgh NMR Center for Biomedical Research, Dr. Stephen Wisniewski in the Dept. of Epidemiology, Dr. Robert Garman of

Consultants in Veterinary Pathology, Inc., Dr. Simon Watkins in the Dept. of Cell Biology and Physiology, Dr. Timothy Billiar in the Dept. of Surgery, Drs. Carleton Hsia and Li Ma, Synzyme of Technologies, and Dr. Samuel Poloyac in the School of Pharmacy for expertise that greatly raises the level of the research at the Safar Center. I thank Dr. John Leventhal for helping with faculty development. I also thank Drs. Richard Bauman and Joseph Long



From left to right: Mrs. Denise Kochanek, Marci Provins, and Fran Mistrick at the dedication of the Safar Conference Room. Fran's monumental efforts produced a historical display that truly captured the incredible career of Dr. Peter Safar.

at the Walter Reed Army Institute for Research for valuable discussions. Special thanks to Drs. Robert Wagner and Joseph Newsome for their outstanding veterinary support.

I would like to acknowledge Drs. Carol Nicholson, Ralph Nitkin, and Michael

Weinrich of the National Center for Medical Rehabilitation Research, Dr. Ramona Hicks at the National Institute of Neurological Disorders and Stroke, Colonel Robert Vandrey, at the United States Army Medical Research and Materiel Command, Dr. Frank Tortella at Walter Reed Army Institute of Research, and Mr. Robert Read at Telemedicine and Advanced Technology Research Center (TATRC) for their efforts on behalf of our Center and its investigators. Thanks are also in order for Dr. Lyn Yaffe. Lyn is a long-time friend of the late Dr. Safar, colleague to all of us, and supporter and collaborator who has contributed enormously to our success.

I also owe a debt of gratitude to Mr. Tore Laerdal of Laerdal Medical and to the late Mr. Hans Dahl of the Laerdal Foundation. Their support of our young investigators has been special for many years. Distinguished Professor Dr. Ake Grenvik has also served for many years as a liaison in this regard for our Center and we are grateful to him for his support.

I would also like to recognize and thank Marci Provins and Paddy Driscoll (from PSD Media Services) for their efforts on the design and layout for this year's annual report.

Finally, fundraising efforts continue for the "Safar Legacy Fund," to provide a core budget for the Center, along with funds to support the "Nancy Caroline Fellowship Award" and, of course, the "Safar Symposium." We have enclosed a pledge card describing those funds in this year's report and thank you in advance for your support. Thanks to each of you who have donated to these efforts. Our total goal for these three programs is an endowment of two million dollars to aid us in keeping alive Dr. Safar's goal of the resuscitation of "hearts and brains too good to die."

I once again look forward to success in 2006/2007 in our investigative efforts to develop new therapies in the field of resuscitation medicine, and thank you for your continued support of our work.

Linda Ryan Administrator at the Safar Center greeting guests for the 4th Safar Symposium.



LATE BREAKING NEWS

As we go to press with this year's report, I am pleased to announce four major developments for the Safar Center for Resuscitation Research. First, I am pleased to announce that Dr. Samuel Tisherman, with the assistance of Dr. Lyn Yaffe and TATRC, appears to have garnered support for the first clinical trial of Emergency Preservation and Resuscitation of otherwise lethally injured trauma victims. Final details of this important development are being worked out and we hope to be able to discuss this further in next year's report.

Second, former fellow and faculty member in the Division of Critical Care Medicine at Children's National Medical Center, Dr. Michael Bell, was recently recruited back to Pittsburgh to join our CCM faculty and the Safar Center. Third, we are pleased that Dr. James Menegazzi in the Center for Emergency Medicine is strongly considering moving his laboratory to the Safar Center. As discussed, Jim's program would be a perfect addition to our Center. Renovation of laboratory space on the second floor of our Center for Jim is being discussed to accommodate Jim's NIH-funded program. Finally, I am extremely pleased to announce that we were asked to partner with investigators at the Walter Reed Army Institute of Research (WRAIR) on a submission to the Defense Advanced Research Projects Agency (DARPA) of the United States Department of Defense addressing the problem of blast-induced traumatic brain injury—which is critical to our combat casualties in the use of improvised explosive devices in the Iraq war and of emerging importance to civilians in the setting of terrorist attacks. We have just been informed that we were selected by DARPA for funding of this important "PREVENT BLAST" research initiative. We thank Dr. Richard Bauman, at WRAIR, for the invitation to participate in this special project. Please look for more in next year's report on these late-breaking developments.

Respectfully submitted,

Patrick M. Kochanek, MD
Director, Safar Center for Resuscitation Research



Patrick M. Kochanek, MD, Director, Safar Center for Resuscitation Research
Director, Traumatic Brain Injury

Hülya Bayır, MD
Associate Director, Oxidative Stress
and Antioxidant Therapy

Rachel P. Berger, MD, MPH
Associate Director, Child Abuse

Clifton Callaway, MD, PhD
Associate Director, Cardiac Arrest

Robert S.B. Clark, MD
Associate Director, Molecular Biology

C. Edward Dixon, PhD
Associate Director, Functional Outcome

Larry W. Jenkins, PhD
Associate Director, Molecular Biology

Anthony E. Kline, PhD
Associate Director, Rehabilitation Research

Samuel A. Tisherman, MD
Associate Director, Shock and Emergency
Preservation and Resuscitation

Amy K. Wagner, MD
Associate Director, Rehabilitation Research

Scientists

P. David Adelson, MD
Nicholas Bircher, MD
Miroslav Klain, MD, PhD
S. William Stezoski

Associate Scientists

Steven DeKosky, MD
Lina Du, MD
Lesley M. Foley, B.Sc.(Hon)
Robert Garman, DVM
Steven Graham, MD, PhD
T. Kevin Hitchens, PhD
Robert Hickey, MD
James J. Menegazzi, PhD
Sam Poloyac, PhD
Ernesto A. Pretto, MD
Ann Radovsky, DVM, PhD
James V. Snyder, MD
Stephen R. Wisniewski, PhD
Lyn Yaffe, MD
Hong Qu Yan, MD

Fellows

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Alia Dennis, MD
Tomas Drabek, MD
Melinda F. Hamilton, MD*
Ericka Fink, MD*
Yi-Chen Lai, MD*
Karen Walson, MD

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Raymond Griffith
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Paula Nathaniel
Jason Stezoski
Vince Vagni

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Amber Casey	Samuel S. Shin
Damian Clossin	Josh Sokoloski
J'Mir Cousar	Chris Sozda
Ashley R. Crumbly	Chris Stangey
Shaun Darrah	Michael Tortorici
Julie Dobos	Matthew Tormenti
Laura Drewnicki	Chris Washington
Jesse Fisk	Mike Wenger
Ashley Grosvenor	Brian Westergom
Rashed Harun	Lauren Willard
Lee Haselkorn	
Annie Hoffman	
Lauren Kmec	
Scott Kunkel	
Matt LaRosa	
Pallavi Luthra	
Rebecca Malena	
Laurie Mohler	
George Nikhil	
Adam Olsen	
Monisha Panda	
Brett Postal	
Zachary Repanshek	

* denotes current T32 fellow

FINANCIAL HIGHLIGHTS

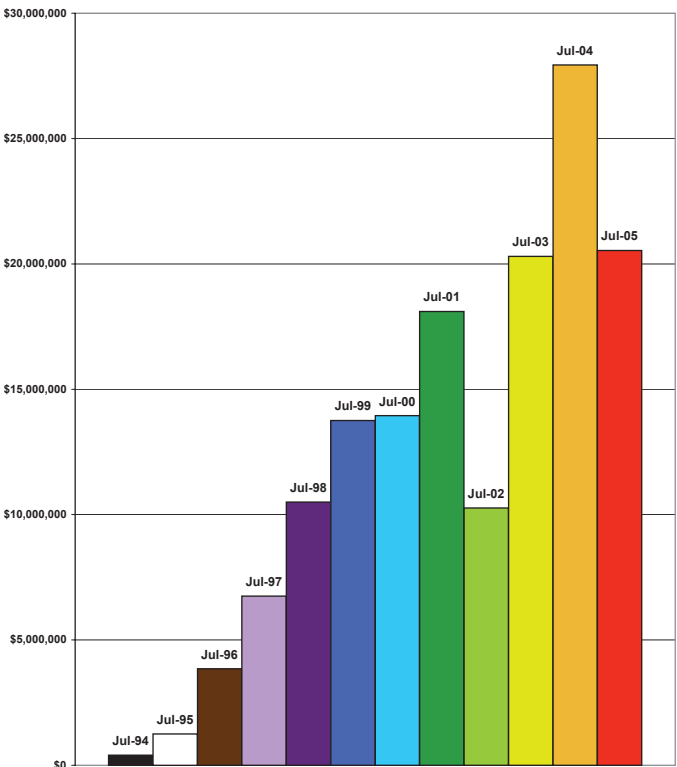
During the 2005/2006 academic year, Safar Center investigators had a total of 36 active grants. Thirty-four of these grants were extramural. The direct and indirect costs for the full award periods of these grants totaled \$20,532,421 and this is plotted below for the current and preceding ten academic years.

The specific sources of support are shown. We continue to maintain a remarkably high level of support, even given the current funding challenges at NIH. This has required a monumental effort by our faculty since our support is almost completely derived from extramural grants. Congratulations to the faculty for their funding successes. Also, as discussed in the opening letter, not reflected yet in the graphs of the 2005 funding that are depicted here are several newly renewed and funded grants including competitive renewal of the long-standing program project award in traumatic brain injury—namely, the University of Pittsburgh Brain Trauma Research Center—a \$5 million, 5-year award from the NINDS, competitive renewal of our T-32 program titled “Training in Pediatric Neurointensive Care and Resuscitation Research” from NICHD, and a new \$2 million award from the United States Army titled “Novel Nitroxide Resuscitation Strategies in Experimental Traumatic Brain Injury.” These new grants will be reflected in next year’s financial report.

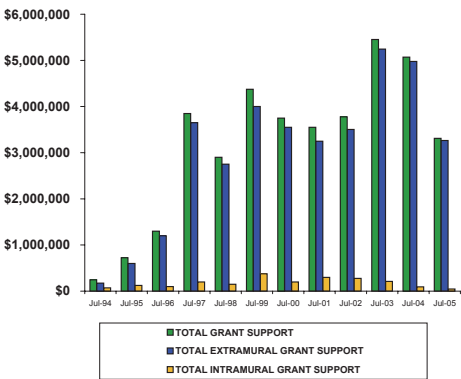
The portion of the budget for use in each academic year (July 1 through June 30) is also plotted for the current and preceding ten academic years on the following page. This represents direct and indirect costs and is shown for total, extramural, and intramural grant support.

Extramural funding sources included the NIH, the Centers for Disease Control and Prevention, the Laerdal Foundation, the American Heart Association-National Affiliate, and other sources. Intramural funding was provided by the Departments of Critical Care Medicine, Anesthesiology, and Pediatrics and the Children’s Hospital of Pittsburgh. We are deeply grateful for this support.

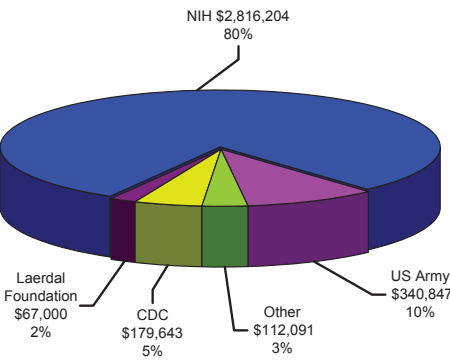
Direct and Indirect Costs for the Full Award Period of SCRR Grants



Safar Center Grant Support through 2005/2006 use in each academic year



Specific Sources of Grant Support 2005/2006



TRAUMATIC BRAIN INJURY (TBI)

In the United States, approximately two million people incur TBI each year, largely as a result of vehicular accidents, falls, acts of violence, and sports accidents. Over 50,000 people die and over 200,000 are hospitalized each year from TBI, at an annual cost of about \$9-10 billion for acute care and rehabilitation. Current treatment is comprised largely of supportive care and the control of raised intracranial pressure. Better understanding of the response of the injured brain is needed as are new treatments.

The Safar Center is, to our knowledge, the only Center in the United States that is funded by program project grants (large programmatic grants linking multiple projects) in the area of TBI from both the National Institutes of Health (NIH) and the United States Army. The program project funded by the NIH is overseen by Safar Center Associate Director, Dr. C. Edward Dixon, and is focused on developing new treatments for TBI based on the study of novel pathways of secondary damage in the injured brain. Some of these studies include investigation of the link between Alzheimer's disease and TBI—with the hope of developing shared therapies for these disorders; the study of new approaches to blocking neuronal death after injury—such as agents targeting energy failure in neurons, mitochondrial dysfunction, PARP activation, oxidative damage, inflammation, calcineurin, apoptosis; and therapies focused on improving functional outcome. Our program project funded by the United States Army is a collaborative effort with Synzyme Technologies of Irvine, California, and is focused on the testing of new resuscitation fluids for the optimal acute stabilization of victims of combined TBI and shock. This program involves testing of novel polynitroxylated albumin and hemoglobin solutions, among other therapies and is discussed further in the section on “Combat Casualty Care.”

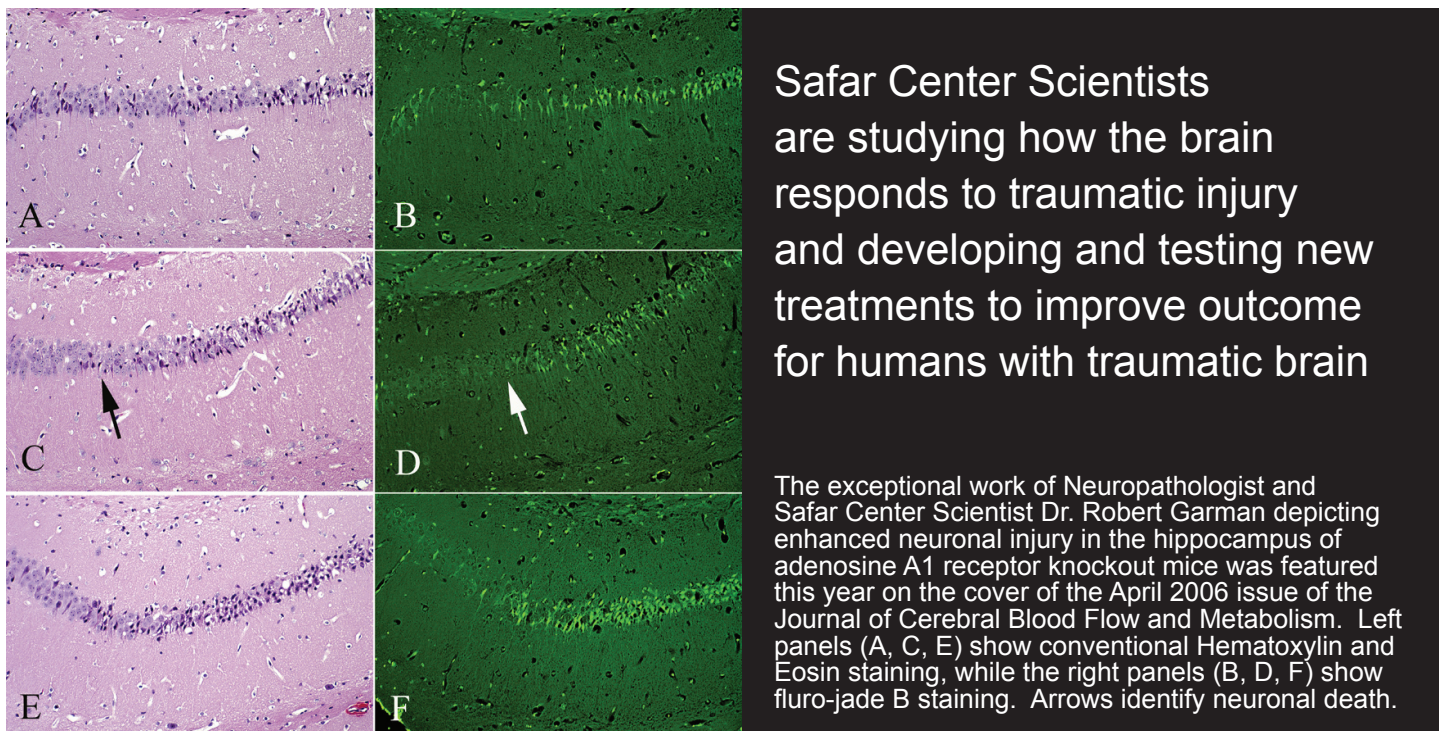
Many other federally-funded projects on TBI are being carried out at the Safar Center. NIH-funded research is directed toward the development of new treatments,

such as agents targeting the adenosine, apoptosis, dopamine, kinases, protein synthesis, or serotonin pathways, among others.

Work on TBI at the Safar Center is also funded by the Centers for Disease Control and Prevention via the University of Pittsburgh Center for Injury Research and Control (CIRCL)—directed by Dr. Hank Weiss in the Dept. of Neurological Surgery. Those studies include investigation by Dr. Amy Wagner of both the impact of gender and hormones on TBI outcomes and clinical trials by Drs. Rachel Berger and Kochanek focused on biochemical detection of missed cases of child abuse (discussed later in this report).

Several projects in TBI focus on head injury in infants and children—including evaluation of novel antioxidant therapies in models of pediatric TBI, and study of biomarkers of secondary damage in the brain in critically ill children with severe TBI at Children's Hospital of Pittsburgh.

We are also linked to the work of Dr. P. David Adelson in the Dept. of Neurological Surgery at Children's Hospital of Pittsburgh who is carrying out clinical studies of therapeutic hypothermia in pediatric TBI. Many of the studies in TBI at the Safar Center interface with other areas of research presented in this report—such as child abuse, combat casualty care, and rehabilitation.



In 2005-2006, Safar Center investigators authored a remarkable 32 peer-reviewed manuscripts on TBI. Among the highlights was publication by T-32 fellow Dr. Paul Shore of a manuscript in the journal *Critical Care Medicine* describing the PILOT scale—a clinical new tool that can be used to assess therapeutic intensity level in infants and children being treated for severe TBI. Also noteworthy, Dr. Kochanek's group published a report demonstrating the unique development of posttraumatic status epilepticus in adenosine receptor knockout mice. Another particularly noteworthy report was produced by Dr. Xiaopeng Zhang working in the laboratory of Dr. Robert Clark who demonstrated caspase-7 activation in human brain in patients with severe TBI. Both of these reports were published in the *Journal of Cerebral Blood Flow and Metabolism*. We are also pleased to report that former Safar Center trainee Dr. Courtney Robertson at the University of Maryland was one of the editors of a special issue of the journal *Developmental Neuroscience* that was devoted to the topic of pediatric TBI. That issue was a relative who's who in the field of traumatic brain injury in infants and children and featured five manuscripts by current Safar Center investigators.

Faculty Principal Investigators

Patrick M. Kochanek, MD
C. Edward Dixon, PhD
P. David Adelson, MD
Hülya Bayır, MD
Rachel P. Berger, MD, MPH
Robert S.B. Clark, MD
Steven T. DeKosky, MD
Weimin Gao, PhD
Steven H. Graham, MD, PhD
Larry W. Jenkins, PhD
Anthony E. Kline, PhD
Amy K. Wagner, MD
Hong Yan, MD

CHILD ABUSE

Inflicted childhood neurotrauma is the most important type of injury in infants resulting from child abuse – commonly known as the shaken baby syndrome. Inflicted childhood neurotrauma is the leading cause of death from TBI in children less than two years of age. More than 1 in 3,000 children less than 1 year of age are victims of severe or fatal inflicted childhood neurotrauma and the number of more mild cases may be over 100 times higher. Recognition of inflicted childhood neurotrauma can be quite difficult for physicians.

This year, Dr. Rachel Berger published an important report in the journal *Pediatrics* that strongly supports the potential use of serum biomarkers to help pediatricians make the critical diagnosis of inflicted childhood neurotrauma. Her work has been called some of the most important research currently underway on the topic of child abuse.

Parents often do not provide a history of trauma, infants present with non-specific symptoms that are seen in common pediatric illnesses, and the physical examination can be normal. The importance of timely diagnosis of this condition cannot be overemphasized.

Rachel Berger, MD, MPH is leading a collaborative team of investigators on an exciting project to provide physicians with an important new tool to aid in making the often difficult diagnosis of inflicted childhood neurotrauma. In a study funded by both the Centers for Disease Control and Prevention (CDC) and the National Institute of Child Health and Human Development, Dr. Berger is evaluating a panel of biomarkers of brain injury using a simple blood test. Similar to the approach taken using biomarkers such as troponin or creatine phosphokinase to aid in diagnosing myocardial

infarction, two promising biomarkers, neuron specific enolase (NSE) and myelin basic protein (MBP) appear to be able to help clinicians recognize silent brain injury in infants presenting to clinic with non-specific signs and symptoms such as irritability, colic, and vomiting, among others. Dr. Berger is being mentored on her K-23 award from the National Institute of Child Health and Human Development by Dr. Kochanek, who is the senior investigator on this CDC-funded research project.

Safar Center investigators are also involved in studies to identify novel biomarkers of brain injury using cerebrospinal fluid and blood samples from children with both inflicted childhood neurotrauma and accidental brain trauma, such as falls or motor vehicle accidents. These studies are being carried out by Drs. Kochanek,

Berger, Clark, Gao, and Jenkins, and include research to identify unique proteins or molecular patterns in samples from injury victims that could have diagnostic or therapeutic value. Studies by Drs. Bayır, Clark, and Jenkins are also ongoing in experimental models of pediatric TBI to develop new therapies for victims of severe brain injury from inflicted and non-inflicted (accidental) childhood neurotrauma, along with unique testing of the effect of therapeutic hypothermia on both intracranial hypertension and long-term outcome in infants with this condition, by Dr. Adelson at Children's Hospital.

In 2005-2006, Safar Center investigators authored seven peer-reviewed manuscripts in the area of child abuse. In addition to Dr. Berger's key report in the journal *Pediatrics*, Drs. Weimin Gao and Larry Jenkins spearheaded completion of a manuscript in press in the *Journal of Neurotrauma* on the use of proteomics to assess cerebrospinal fluid protein expression to compare infants with inflicted versus non-inflicted childhood neurotrauma. Dr. Berger also published a manuscript that describes the comparison between serum biomarker levels across three important diseases in pediatric neurointensive care, namely inflicted and non-inflicted childhood neurotrauma and cardiac arrest. Remarkably, there are more similarities in the biomarker patterns observed after inflicted childhood neurotrauma and cardiac arrest—suggesting a key role for hypoxic-ischemic injury in the child abuse victims. That work was published in the journal *Developmental Neuroscience*. I am also pleased to report that a manuscript discussed in last year's annual report by Dr. Margaret Satchell describing increases in the mitochondrial protein cytochrome-c in cerebrospinal fluid of victims of inflicted childhood neurotrauma has become one of the most highly cited papers in 2005 in the *Journal of Cerebral Blood Flow and Metabolism*.

Faculty Principal Investigators

Rachel P. Berger, MD, MPH

P. David Adelson, MD

Hülya Bayır, MD

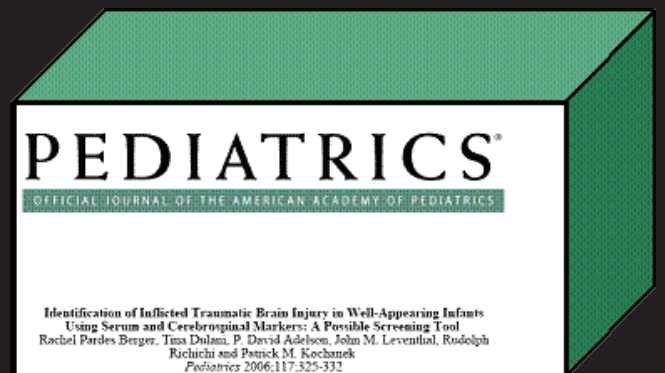
Robert S.B. Clark, MD

Weimin Gao, PhD

Larry W. Jenkins, PhD

Patrick M. Kochanek, MD

“A misdiagnosed infant with inflicted childhood neurotrauma is likely to return to a violent environment where he or she may be re-injured or killed.”





Cardiac arrest is an enormous public health problem. There are an estimated 330,000 out-of-hospital cardiac deaths per year in the United States. Overall survival rate from cardiac arrest is estimated to be about 6%. Resuscitation currently results in return of spontaneous circulation in less than 40% of arrest victims, and only about 10% of victims ever regain consciousness. There is also a substantial incidence of in-hospital cardiac arrests and fewer than 20% of these victims survive to hospital discharge.

Drs. Clifton Callaway and Samuel Tisherman lead the University of Pittsburgh's participation in the NIH-funded Resuscitation Outcomes Consortium which is evaluating new therapies to improve outcome after cardiac arrest in humans.

Research by Safar Center investigators on the topic of cardiac arrest builds on the pioneering work of the late Dr. Peter Safar, the father of modern resuscitation and innovator who developed mouth-to-mouth resuscitation and spearheaded the implementation of modern-day CPR. Work in this program involves research on three separate fronts—sudden cardiac arrest in adults, asphyxial cardiac arrest in infants and children, and exsanguination cardiac arrest in trauma victims.

Cardiac arrest and resuscitation in adults

Dr. Clifton Callaway is the overall director of the cardiac arrest program at the Safar Center. His research is focused on sudden cardiac arrest in adults and is carried out at the University of Pittsburgh Center for Emergency Medicine to which he has created an important link to the Safar Center. In work funded by the American Heart Association and the NIH, Dr. Callaway's bench to bedside work ranges in scope from the study of the mechanisms underlying neuronal damage after cardiac arrest in experimental animal models to clinical trials of new therapies.

Highlights this year from his group include two reports in the journal *Resuscitation*, one on the effects adenosine A1 receptor antagonists on ventricular fibrillation waveform morphology in experimental cardiac arrest and another on inter-rater reliability for bystander CPR.

In related work, PhD candidate Michael Tortorici, working under the superb mentorship of Dr. Sam Poloyac in the University of Pittsburgh School of Pharmacy, published an interesting manuscript in the journal *Critical Care Medicine* describing the potent effects of therapeutic hypothermia on cytochrome-P450 mediated drug metabolism. That manuscript and other ongoing collaborative work between our Center and Dr. Poloyac's group are helping to define the importance of careful titration of emergency and intensive care of patients managed with therapeutic hypothermia after cardiac arrest.

Cardiopulmonary arrest in infants and children

Dr. Robert Clark leads a team of investigators at the Safar Center and Children's Hospital of Pittsburgh that is focused on the development of new therapies to mitigate neurological damage after asphyxial arrest in children. Unlike adults,

Drs. Valerian Kagan and Hülya Bayır (front, left to right, and Yulia Tyurina and Vladimi Tyurin, back, left to right) are studying exciting novel pathways of oxidative damage to mitochondria that trigger neuronal death via apoptosis in the developing brain after cardiac arrest. Their use of oxidative lipidomics in CNS injury represents a breakthrough approach to unraveling the important role of oxidative stress in both the lab and the ICU.



Dr. Samuel Poloyac and his team from the School of Pharmacy are studying the effect of therapeutic hypothermia on drug metabolism after cardiac arrest. A better understanding of the side effects of hypothermia will greatly help us best use this important therapy.

who suffer cardiac arrest generally as a result of myocardial infarction and ventricular fibrillation, children suffer asphyxial insults such as drowning, suffocation, SIDS, and apnea.

This year, Safar Center Associate Director Dr. Hülya Bayır was awarded a Scientist Development Award from the American Heart Association National Affiliate. She is using a model of asphyxial cardiac arrest in rats developed at the Safar Center to study novel aspects of oxidative stress in the injured brain. Her work is also being done in collaboration with Dr. Valerian Kagan, Director of the Pittsburgh Center for Free Radical and Antioxidant Health. They have reported important findings on oxidative damage to the mitochondrial lipid cardiolipin that result in the release of cytochrome-c. This provides a link between oxidative stress and apoptosis at the level of mitochondrial triggers. Also, Dr. Ericka Fink was awarded a K-12 award from the NICHD to study the role of poly-ADP ribose polymerase in pediatric cardiac arrest. She is a new faculty member working under the direction of Dr. Clark and is also assembling a clinical database of pediatric cardiac arrest cases at Children's Hospital.

Exsanguination cardiac arrest

Cardiac arrest from exsanguination is a unique and important condition that has special relevance in trauma care. Penetrating trauma—such as gunshot wounds—can lead to rapid exsanguination with cardiac arrest that occurs in both the civilian and military settings. Drs. Samuel Tisherman and Patrick Kochanek have been studying exsanguination cardiac arrest as a key target of the novel resuscitation approach—EPR—that was previously discussed in the opening letter. Additional discussion of research targeting exsanguination cardiac arrest is provided below in the section focused on EPR.

Faculty Principal Investigators

Clifton Callaway, MD, PhD	Robert S.B. Clark, MD
Hülya Bayır, MD	Ericka Fink, MD
Robert Hickey, MD	Patrick M. Kochanek, MD
Samuel Poloyac, PharmD, PhD	Samuel A. Tisherman, MD

EMERGENCY PRESERVATION AND RESUSCITATION (EPR)

Despite the millions of lives saved through the pioneering development and implementation of CPR by Dr. Safar and associates, and its world-wide implementation facilitated by the development of Resusci-Anne by Mr. Asmund Laerdal and Dr. Bjorn Lind, a number of key challenges remain in the field of resuscitation. One important type of insult that continues to have a nearly 100 percent mortality is exsanguination cardiac arrest. This condition is not only the leading cause of death of potentially salvageable combat casualties, but is also an important cause of death in civilian trauma.

Our work on EPR was featured as one of the top ideas of the year in the December 2005 issue of *New York Times Magazine* “Year in Ideas,” and was also featured in *U.S. News and World Report*.

In 1984 Dr. Safar with advice from Colonel Ronald Bellamy, the foremost authority on combat casualties during the Vietnam conflict, developed a revolutionary new concept targeting battlefield death from rapid exsanguination. This approach involved transient “preservation” of the victim—to allow evacuation, transport, and emergency “damage control” surgery, followed by a delayed resuscitation using cardiopulmonary bypass. This concept was first described in the literature by Dr. Tisherman and co-workers in 1990 in a manuscript in the *Journal of Trauma* where the concept was called “deep hypothermia for preservation and resuscitation.” Shortly thereafter, it was called “Suspended animation for delayed resuscitation” and eventually EPR.

Studies at the Safar Center have taken this concept from theory to reality. The first report of this work used a rapid aortic flush after exsanguination cardiac arrest in a dog model and demonstrated that up to 30 minutes of preservation could be achieved with intact neurological outcome. In these pioneering studies, emergency preservation was achieved by rapid cooling to about 7°C, and resuscitation was achieved using cardiopulmonary bypass with slow re-warming.

Subsequent studies in our center demonstrated that emergency preservation could be achieved with intact outcome after cardiac arrests of as long as 3 hours in duration—and possibly longer. This approach has now been demonstrated across multiple species (rats, pigs and dogs) and in multiple laboratories including Drs. Wilhelm Behringer and Fritz Sterz at Vienna General Hospital, and Dr. Hasan Alam at Harvard Medical School.

The EPR program is directed by Drs. Tisherman and Kochanek at the Safar Center. This year, former fellow Dr. Xianren Wu published an important report on EPR in the journal *Circulation*, demonstrating that EPR is effective even when it is preceded by a prolonged period of hemorrhagic shock—two hours in this case. Dr. Wu also has reported, in abstract form,

A WINTER'S SLEEP

Hibernation's secrets may help treat a host of human afflictions

By Katherine Hobson

Hibernation seems simple enough: Animals fatten up in the summer, disappear into their dens during the winter, when food is scarce, then emerge in the spring alive and alert, if a lot thinner. But if you could peek inside a hibernating ground squirrel, you'd witness a physiological wonder. The animal's metabolism slows to almost nothing. Its body temperature plummets to a few degrees warmer than outside. Its heart-beat slows from 300 beats per minute to fewer than 10. And other, more mysterious changes protect the squirrel in a state that would kill many other animals.

It's that self-protection that intrigues medical researchers. Figuring out how mammals survive such extreme conditions offers clues to how humans might be protected against their own health threats. Fueling interest in the field is a recent paper published in *Science* showing that mice—which don't hibernate—were induced to do so by a calibrated whiff of a normally toxic gas. When the gas was removed, the mice emerged apparently unharmed from their sluggish state. While any human applications are years away, says the paper's lead author, Mark Roth, of the Fred Hutchinson Cancer Research Center in Seattle, a group of venture capitalists is hopeful enough to invest \$10 million in a start-up company. Here is a sampling of medical problems that hibernation research is addressing:

Organ preservation. A big problem in organ transplantation is time. Lacking fresh blood, even cooled organs quickly become unusable. So scientists are looking at what protects the organs of hibernating animals even during periods of very low blood flow. Tsung-Ping Su, at the National Institute on Drug Abuse, heard from a colleague about a protein from a hibernating woodchuck that seemed to have the same pain-fighting ability as opioids like morphine. He found that a synthetic version could in-



Does this hibernating arctic land squirrel carry clues that could someday help emergency medical workers?

U.S. & WORLD REPORT U.S. News

duce a ground squirrel to go into hibernation off schedule. Su, working with a cardiac surgeon, discovered that a dog's lung preserved with the substance survives longer than one bathed in a control solution, raising the possibility for use in human organs.

Stroke. Most strokes are caused by a blocked blood vessel to the brain, which starves brain cells. But the brains of hibernating animals somehow survive restricted blood flow. "Metabolism slows so much that cells think they're in hypoxia and turn on a response that helps tissues survive," says Kenneth Storey, a molecular physiologist at

with a trauma surgeon, to design potential human trials.

Osteoporosis. When our bones don't bear weight for a long time, they become brittle. That's what happens to astronauts and to the bedridden. But hibernating bears loll around for months, and yet in the spring their bones are as strong as ever. Researchers think bears recycle the calcium lost from inactivity by recapturing it in the blood and using it to rebuild bone. Seth Donahue, a biomedical engineer at Michigan Technological University, is part of a group analyzing changes in blood hormone levels of hibernating black bears to identify what is

nonhibernating squirrels and shown that the hibernating ones were less sensitive to removing nutrients like glucose, even at normal temperatures.

If a substance were isolated, it might buy stroke victims some time. "If you could turn off metabolism right away—if the EMT had something to inject—you could turn off the demand for blood flow," says Kelly Drew of the Institute of Arctic Biology at the University of Alaska-Fairbanks.

Trauma. Soldiers in combat and gunshot victims often bleed to death from their wounds. Instead of focusing on increasing blood supply through transfusions, Patrick Kochanek is looking at rapidly reducing the body's demand, potentially giving medics time to evacuate or treat the victim. With collaborators, Kochanek, director of the Safar Center for Resuscitation Research at the University of Pittsburgh, replaced the blood of wounded dogs with a near-freezing saline solution that cooled their brains to as little as 7 degrees Celsius. The dogs stopped breathing, and their hearts stopped. But two hours later, when they were reinfused with blood and had recovered, they were fine. Kochanek is now working



"If you could turn off metabolism right away...you could turn off the demand for blood flow."

Kelly Drew, University of Alaska-Fairbanks

supercharge their bone building right after hibernation. The long-term goal is to treat all human osteoporosis, not just that caused by disuse.

Direct human use of hibernators' secrets is years off, and it's unlikely that we'll ever regularly spend months in a state of extreme torpor. But our basic similarity to these animals is close enough to make their protective tricks theoretically applicable. "Thus far, there don't seem to be any special gene products that are unique to the mammals that hibernate," says Hannah Carey, a physiologist at the School of Veterinary Medicine at the University of Wisconsin-Madison. Last year, scientists reported hibernation behavior in one species of lemur—a primate, like humans. It all adds to the promise that the outwardly simple process of hibernation will yield answers to some of medicine's most complex problems. ■

results of exciting work that has demonstrated the remarkable 3 hours of EPR can be achieved with the addition of dissolved oxygen and glucose to the flush solution. More on that seminal work in next year's report.

In addition, as we went to press, Dr. Tomas Drabek's work describing the development of the first rat model of EPR has appeared in the journal *Critical Care Medicine*. This new model has great potential to allow us to screen drugs that may augment the benefits of hypothermia—allowing us to extend the EPR duration or consider using less drastic levels of hypothermia.

Dr. Samuel Tisherman has submitted a proposal for federal support of the first feasibility trial of EPR in human trauma victims that have otherwise lethal insults from exsanguination cardiac arrest. We hope to have more details on this proposal in next year's report.

Drs. Kochanek, Tisherman, Wu, Yaffe and Mr. Stezoski were granted a patent through the University of Pittsburgh School of Medicine on the most recent EPR method and a kit to facilitate its induction.

Faculty

Samuel A. Tisherman, MD
Patrick M. Kochanek, MD

S. William Stezoski
Miroslav Klain, MD

HEMORRHAGIC SHOCK

Hemorrhagic shock is a leading cause of death in civilian and military trauma and the Safar Center has a rich history of resuscitation research in this area of study. Hemorrhagic shock can lead to either acute death from exsanguination or delayed morbidity and/or mortality from multiple organ failure. The program on hemorrhagic shock at the Safar Center is directed by Dr. Samuel Tisherman and has focused on the use of clinically-relevant models of hemorrhagic shock to evaluate novel resuscitation strategies. These models were designed by Dr. Tisherman and the late Dr. Safar, along with a number of research fellows in our center, and have carefully implemented shock/trauma, field resuscitation, and hospital resuscitation phases, to study therapies throughout the continuum of care. Clinically relevant uncontrolled hemorrhage is incorporated into many of these models to simulate the ongoing uncontrolled bleeding during the shock phase.

Although a number of therapies for hemorrhagic shock have been tested and developed by investigators at the Safar Center, the most promising treatment, which has been shown to be effective in many studies, is mild hypothermia. Mild hypothermia mitigates deleterious cardiovascular effects and cell death cascades during and after shock, and prolongs the golden hour. However, this work has raised controversy in the shock community, since hypothermia is associated with poor outcome in patients with hemorrhagic shock. Key differences between induced and “spontaneous” hypothermia, however, may help explain these controversies. Although cooling is protective against tissue ischemia during and after shock, it also has adverse effects on coagulation that may be magnified by the use of crystalloid resuscitation fluids and packed red blood cells, both of which dilute the natural clotting mechanisms. The need for factor replacement or other related pro-coagulant approaches

“The goal of this program is to prolong the golden hour of shock and allow survival with good outcome for trauma victims.”



Dr. Tomas Drabek is a visiting clinician-scientist who is studying novel therapeutic approaches for victims of otherwise lethal exsanguination, including hypothermia, new drugs, and potential agents to induce hibernation-like states.

may allow the use of mild cooling to protect against ischemic damage. Optimization of mild hypothermia is an important area of future research

Other unique therapies that we have studied include intraperitoneal delivery of oxygen, cooling, and drugs (such as adenosine). Some of these approaches have produced exciting findings and are under continued study. This year, Dr. Tomas Drabek has been studying novel

agents to induce hypothermia in pigs that might serve as hibernation-like triggers to protect in hemorrhagic shock. Investigation on this work is ongoing.

Faculty

Samuel A. Tisherman, MD

COMBAT CASUALTY CARE

There is a long-standing relationship between the Safar Center for Resuscitation Research and the United States Department of Defense. That relationship was initiated in the late 1950s as a result of Dr. Safar's pioneering work on the development and implementation of CPR—which was funded by a grant from the United States Army.

A number of the research programs at the Safar Center are relevant to the development of new resuscitation advancements in the setting of combat casualty care. Investigators at our Center have worked with the United States Department of Defense which has funded a number of its projects targeting the spectrum of trauma resuscitation. The aforementioned novel program on EPR is just one of many examples where we have collaborated with experts from the United States Military to work toward the goal of saving lives of combat casualties. Our research in the areas of traumatic brain injury, hemorrhagic shock, combinations of these insults, and most recently,

participation in the upcoming DARPA-funded PREVENT BLAST initiative, is highly relevant to combat casualty care. Each of these projects is relevant to both military and civilian trauma resuscitation.

We have been supported over the years by grants from the United States Army, including the Telemedicine and Advanced Technology Research Center (TATRC), the United States Naval Medical Research Institute, and The United States Congress and we have worked closely under the oversight of each of these agencies on all of the individual projects. Our work on EPR, funded initially by the United States Navy and later by the

United States Congress and TATRC are examples of United States Department of Defense supported research at the Safar Center. We have also received valuable consultative input from military experts, both active and retired.

Targeting Blast-Induced Brain Injury: The New Epidemic in Combat Casualty Care

Exciting new research in our center includes a new program project funded by the United States Army Peer Reviewed Medical Research Program (PRMRP) titled "Novel Nitroxide Resuscitation Strategies in Experimental Traumatic

Our goal is to develop a resuscitation strategy that limits shock while conferring maximal neuroprotection.

Brain Injury.” This is a collaborative effort with Drs. Carleton Hsia and Li Ma at Synzyme Technologies of Irvine, California. This research project includes the development of a new clinically-relevant experimental model of traumatic brain injury combined with hemorrhagic shock. This model targets blast-induced brain injury—an emerging epidemic in both military and civilian trauma from terrorist attacks. Often, the improvised explosive devices (IEDs) produce the devastating combination of traumatic brain injury and hemorrhage from either severe blast injury to trunk or extremities or penetrating trauma from shrapnel (i.e., bolts, screws, and other types of metal fragments) within the IEDs. We are examining conventional and novel resuscitation strategies targeting this important problem. Novel polynitroxylated albumin and hemoglobin solutions, among other conventional and novel therapies are under evaluation. This work includes important additional collaborations with the Pittsburgh NMR Center for Biomedical Research at Carnegie Mellon University, directed by Dr. Chien Ho, Veterinary Neuropathologist Dr. Robert Garman, and the University of Pittsburgh Center for Free Radical and Antioxidant Health, directed by Dr. Valerian Kagan.

In the early stages of work on this grant, we have developed a new and exciting model of combined traumatic brain injury and hemorrhagic shock in mice. Studying this combination in mice is unique and

we believe opens up investigation of this area to the use of valuable transgenic and knockout strategies—which should provide important new mechanistic and therapeutic insight into this complex and important combined insult. Pediatric Critical Care Medicine fellow Dr. Alia Dennis is currently working on the development of this model and we hope to have more information on this new area of study in next year’s annual report.

Faculty

Patrick M. Kochanek, MD

Samuel A. Tisherman, MD

Hülya Bayır, MD

Robert S.B. Clark, MD

C. Edward Dixon, PhD

Larry W. Jenkins, PhD



Dr. Alia Dennis is developing a clinically realistic model of combined traumatic brain injury and hemorrhagic shock in mice to screen novel resuscitation strategies for victims of blast-induced traumatic brain injury and polytrauma.

Blast-induced traumatic brain injury is an important emerging problem in victims of terrorist attacks both in the military and civilian sectors.

REHABILITATION OF CENTRAL NERVOUS SYSTEM INJURY

Inclusion of a comprehensive research program in rehabilitation of central nervous system injury is an important and unique component of the Safar Center. Investigators in our center have been increasingly interested in strategies to improve long-term outcome for CNS insults such as TBI and cardiopulmonary arrest. Thus, inclusion of investigators in the Dept. of Physical Medicine and Rehabilitation (PM&R) of the University of Pittsburgh School of Medicine is essential. This is part of the shared vision of Drs. C. Edward Dixon, Ross Zafonte (Chairman of the Dept. of PM&R), and Patrick Kochanek, and has led to a synergistic and highly productive collaboration.

In addition to the many studies of acute interventions for cerebral resuscitation being carried out at the Safar Center, we are evaluating the efficacy of rehabilitation-relevant therapies in the sub-acute and delayed periods after brain injury. This represents an exciting avenue of research that will take maximal advantage of the unique brain injury models that are available at the Safar Center.

This year, in work funded by the CDC through the University of Pittsburgh Center for Injury Control and Research, Dr. Amy Wagner, a Physiatrist in the Dept. of PM&R has generated important clinical data on the hormonal response to severe traumatic brain injury in adults. She has, for the first time, serially evaluated and

compared progesterone, estrogen, and cortisol levels in both cerebrospinal fluid and serum in these patients. Her findings should provide important new insight in this area as multi-center clinical trials of the promising therapeutic agent progesterone.

Studies are also underway that are examining long-term disturbances in neurotransmitter systems such as the serotonergic, dopaminergic and cholinergic systems—assessing both acute and long-term changes in molecular biology and function, and this year, Dr. Wagner published a report in *Experimental Neurology* on posttraumatic changes in striatal dopaminergic neurotransmission using cyclic voltametry.



Emily Rogers, a talented undergraduate at the University of Pittsburgh, working under the mentorship of Dr. Amy Wagner, published a first author paper on gender and neuroprotection in the *Journal of Head Trauma Rehabilitation*.

The clinicians and scientists with expertise in Physical Medicine and Rehabilitation on our faculty place our Center in the unique position to address all aspects of resuscitation research from the field, through the emergency department, intensive care unit, and through to long-term rehabilitation.

Aspects of CNS injury from trauma or cardiopulmonary arrest appear to share important similarities with a number of chronic neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease, and a spectrum of rehabilitation-related therapeutic strategies including physical interventions, novel pharmacological agents, and stem cell therapy are being evaluated.

Finally, the state-of-the-art functional outcome testing center for evaluation of behavioral outcome in animals is under the direction of Dr. C. Edward Dixon in the Safar Center and includes four Morris water mazes, and other important tools for assessment of long-term

motor and cognitive outcome. It has been instrumental to all of the studies in our center evaluating long-term functional outcome. Several new tools for evaluation of functional outcome are under development in our Center, along with incorporation of other established testing modalities for use in our Center.

Faculty

C. Edward Dixon, PhD

Anthony E. Kline, PhD

Amy K. Wagner, MD

TRAINING

The Safar Center for Resuscitation Research has a rich history of training young investigators in resuscitation-related research, particularly in the field of cerebral resuscitation. Research training was a hallmark of Dr. Safar's illustrious career and this tradition continues as a centerpiece in the Safar Center. Many of our trainees have gone on to become independent investigators — including both NIH-funded scientists and clinician-scientists in the United States, and also funded investigators in major medical centers around the globe.

Established investigators such as Drs. Fritz Sterz and Wilhelm Behringer at Vienna General Hospital, Sven-Erik Gisvold at the University Hospital of Trondheim, Norway, Robert Clark at Children's Hospital of Pittsburgh, Samuel Tisherman at the University of Pittsburgh School of Medicine, Michael Whalen at Massachusetts General Hospital, Michael Bell (who is re-joining our group after several years as faculty at Children's Hospital National Medical Center), Akira Takasu at National Defense Medical College in Saitama, Japan, and Sten Rubertsson, Uppsala University, among others trained in the laboratories of Safar Center investigators.

Postdoctoral fellow positions are funded by several means including 1) individual grants to principal investigators in the Center, 2) individual fellowship grants to trainees, 3) a unique T-32 grant from the National Institute of Child Health and Human Development titled "Pediatric Neurointensive Care and Resuscitation Research," or 4) support from the Laerdal Foundation. The T-32 program evolved out of a long-standing relationship between the Safar Center and the division of Pediatric Critical Care Medicine at Children's Hospital of Pittsburgh. That division, directed by Dr. Ann Thompson, has been one of the leading programs in the world for training clinician-scientists in the field. This relationship has brought a number of very talented young pediatric intensive care clinicians to the Safar Center for research training during their three year fellowship. The generous funding of fellow research at our center over the years by the Laerdal Foundation has also been of great importance to our center and we are pleased to report that a new "Safar Fellowship" stipend has been established by the Laerdal Foundation to support young investigators in Scandinavian countries who are interested in carrying out research training at the Safar Center.

In the last 6 years, 10 trainees at the Safar Center (listed below) have gone on to achieve RO-1s, K-awards, or other substantial national funding, a testament to the strong commitment to research training in the Center. We look for great achievement from these individuals in the years to come.

Hülya Bayır, MD
Michael J. Bell, MD
Rachel P. Berger, MD, MPH
Ericka Fink, MD
Anthony E. Kline, PhD

Trung Nguyen, MD
Courtney L. Robertson, MD
Kimberly D. Statler, MD, MPH
Amy K. Wagner, MD
Michael J. Whalen, MD



Three of our highly successful T-32 trainees, from left to right: Drs. Melinda F. Hamilton, Yi-Chen Lai and Ericka Fink. Drs. Hamilton and Fink have joined our faculty, while Dr. Lai is now an Assistant Professor of Pediatrics in the Division of Critical Care Medicine at the Baylor College of Medicine.

The Safar Center also serves as a resource for research training for interested individuals at all levels, including residents in medical and surgical training, undergraduates, and high-school students. We actively participate in the medical school and undergraduate summer student programs, and also in the minority research programs supported by the University of Pittsburgh.

This year our trainees made a number of important discoveries in their research and garnered several prestigious awards. Details of these outstanding accomplishments are outlined in the opening letter from the Center's director. Congratulations to our many post-doctoral fellows in training for their many accomplishments. Upon completion of their training, these fellows are highly sought after by other programs throughout the US and abroad.

A number of students working with Safar Center Investigators had special achievements this academic year. A few highlights among the many notable accomplishments; Emily Rogers published a manuscript in the *Journal of Head Trauma Rehabilitation* on gender and TBI under the mentorship of Dr. Amy Wagner in our Rehabilitation Program. Emily has done a terrific job this year. J'Amir Cousar published a manuscript in the journal *Developmental Neuroscience* on heme oxygenase in pediatric TBI under the mentorship of Dr. Robert Clark. Finally, Michael Tortorici, while working on his PhD in the School of Pharmacy, published a manuscript on the effect of hypothermia on drug metabolism in experimental cardiac arrest. Michael has been extremely productive and exemplifies the multidisciplinary collaborative nature of research at the Safar Center. Congratulations to these students for first author manuscripts in high quality journals, and to all of the students for their accomplishments.

We are always interested in receiving applications and inquiries from interested young investigators at every level.

THE 26TH PETER AND EVA SAFAR ANNUAL LECTURESHIP IN MEDICAL SCIENCES AND HUMANITIES

On June 28, 2006, Dr. Anthony Atala, W.H. Boyce Professor and Director of the Wake Forest Institute for Regenerative Medicine, and Chair of the Department of Urology at the Wake Forest University School of Medicine served as the 26th Peter and Eva Safar Lecturer in Medical Sciences and Humanities at the University of Pittsburgh School of Medicine.

Dr. Atala is a surgeon in the area of pediatric urology and a researcher directing an impressive group working in the area of regenerative medicine and tissue engineering. His current work focuses on growing new human cells, tissues and organs (including kidney, blood vessels, cartilage, muscle, bladder, pancreas, and others) to repair or replace tissues or organs damaged by age, cancer, trauma, or abnormal development. His presentation was truly spectacular and highlighted his vision of the future of regenerative medicine and tissue engineering and described many exciting findings from a series of extremely high quality publications from his talented group at the Wake Forest Institute for Regenerative Medicine. Many attendees commented that it was the best lecture that they have ever attended.

Mrs. Eva Safar, Dr. John Williams (Chairman of the Department of Anesthesiology) and I would like to express our appreciation to Dr. Atala for his outstanding presentation. The Safar Lecture is supported by an endowment in the Department of Anesthesiology.



Anthony Atala, MD

Dr. Anthony Atala's group at the Wake Forest Institute for Regenerative Medicine is leading the way in translational work in surgical applications of tissue engineering, particularly in the area of Urology. His work is revolutionizing patient care in Urologic surgery.

THE 4TH SAFAR SYMPOSIUM

The Safar Symposium has become an annual tradition at the University of Pittsburgh School of Medicine and features a day of presentations focused in two areas, namely “Breakthroughs in Resuscitation” and “Advances in Human Simulation Education.” The Symposium, thus, features leaders in the respective fields of resuscitation and medical simulation.

On June 28, 2006, the Safar Center hosted the 4th Safar Symposium at the University of Pittsburgh School of Medicine. The symposium also included presentation of the annual Nancy Caroline Award—which is traditionally presented to the top fellow trainee at the Safar Center, as selected by the Associate Directors of the Center, and is linked to the Peter and Eva Safar Lectureship.

The session on “Advances in Resuscitation Medicine” focused on the role of mitochondrial failure in the post-resuscitation syndrome and featured presentations by Dr. Gary Fiskum, Professor and Vice Chair for Research, Department of Anesthesiology, University of Maryland on “Resuscitative Hyperoxia: Too Much of a Good Thing Can Hurt,” Dr. Miguel Perez-Pinzon, Associate Professor of Neurology, University of Miami, “Protein Kinase C, Mitochondria and Cerebral Ischemia,” Dr. Yi-Chen Lai, Fellow, Safar Center for Resuscitation Research, University of Pittsburgh, “Mitochondria, PARP and Energy Failure: A Novel Perspective,” and Dr. Ross Bullock, Reynolds Professor, Division of Neurosurgery, Virginia Commonwealth University, “Cyclosporin in Traumatic Brain Injury: Preliminary Clinical Findings.”



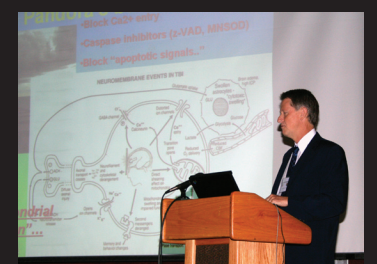
Dr. Gerald Moses of the Telemedicine and Advanced Technology Research Center (TATRC) at Fort Detrick, Maryland described the TATRC perspective on advanced technologies applied to health care.

Speakers at the afternoon session on “Advances in Human Simulation Education” included Dr. Gerald Moses, Lead, Clinical Applications Area of the TATRC, USAMRMC, “Advanced Technologies Applied to Health Care: A TATRC Perspective,” Dr. Mark Scerbo, Professor, Human Factors, Department of Psychology, Old Dominion University, “Enhancing Simulation-Based Training in Medicine Through Virtual Environments,” Dr. Paul Rogers, Professor, Critical Care Medicine, University of Pittsburgh School of Medicine, “Dying 1,000 Deaths for Critical Care Trainees,” Dr. Dave Metro, Assistant Professor of Anesthesiology, University of Pittsburgh School of Medicine, “Simulation as a Tool for Difficult Airway Management Training,” and Mr. John O'Donnell, Director, Nurse Anesthesia Program, University of Pittsburgh School of Medicine, “Back Injury Prevention and Other Nursing Initiatives—Methodology and Approaches in Simulation.”



Dr. Yi-Chen Lai (right) at the Safar Symposium receives Nancy Caroline Award as the top fellow in 2005/2006 at the Safar Center from Dr. Patrick Kochanek (left).

The symposium was attended by over 120 participants. We are grateful to the United States Army Telemedicine and Advanced Technology Research Center for their support of this symposium. Funding was also provided by the Safar Legacy Fund, as well as the Departments of Anesthesiology, and Critical Care Medicine. The afternoon session was hosted by Dr. Paul Phrampus, Director of WISER.



Top to bottom, Drs. Miguel Perez-Pinzon, Gary Fiskum, and Ross Bullock addressed the critical topic of mitochondrial failure in cerebral resuscitation at the 4th Safar Symposium.

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In 2003, the Safar Center for Resuscitation Research initiated the “Safar Legacy Fund,” “The Nancy Caroline Fellow Award,” and “The Annual Safar Symposium” at the University of Pittsburgh to help us in following through with Dr. Peter Safar’s vision for our Center.

We gratefully acknowledge the generosity of the following donors during the fiscal years 2005 and 2006.

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(over)

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