SAFAR CENTER FOR RESUSCITATION RESEARCH





Department of Critical Care Medicine University of Pittsburgh - School of Medicine

Dr. Dele The on Drs Cy

he 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-feet freestanding research facility that houses the laboratories of scientists and clinician-scientists working across a broad spectrum of fields important to resuscitation medicine.

SAFAR CENTER FOR RESUSCITATION RESEARCH

2006/2007 Annual Report

Letter from the Director	2
Directory	10
Financial Highlights	11
Programs:	
Traumatic Brain Injury	12
Cardiac Arrest	14
Child Abuse	16
Emergency Preservation and Resuscitation	17
Hemorrhagic Shock	18
Rehabilitation of Central Nervous System Injury	19
Combat Casualty Care	20
Training	
27th Peter & Eva Safar Annual Lectureship	
5th Safar Symposium	
Bibliography	
Donor Recognition	

Featured on the cover: Five Safar Center trainees received awards at the 2006 Congress of the Society of Critical Care Medicine (SCCM). Pictured from left to right: Ajit A. Sarnaik, MD; Alia M. Dennis, MD; M. Lee Haselkorn; Ava Puccio, RN; and Craig M. Smith, MD.

LETTER FROM THE DIRECTOR



This was another great year for our investigative team at the Safar Center for Resuscitation Research. I am especially pleased that we are continuing to grow and expand now in our 28th year of operation and my 12th year as Center director.

Our scientists and trainees work across a wide number of topics in resuscitation medicine including traumatic brain injury, child abuse, cardiac arrest, emergency preservation, combat casualty care, and rehabilitation. These individuals come from a number of departments in the University of Pittsburgh School of Medicine/ University of Pittsburgh Medical Center (UPMC) including Critical Care Medicine, Neurological Surgery, Physical Medicine and Rehabilitation (PM&R), Surgery, Pediatrics, Anesthesiology, and Emergency Medicine, along with the Schools of both Nursing and Pharmacy. It is exciting to see that the multidisciplinary model that the late Dr. Peter Safar established continues to flourish in our Center.

This year, there were many notable accomplishments at the Safar Center, but I would like to highlight four particularly noteworthy achievements. First, many of the scientists in our center along with several of our key collaborators were selected to participate in the PREVENT blast injury project funded by Defense Advanced Research Projects Agency (DARPA) of the United States



Dr. Rachel Berger was selected as one of the top forty people under the age of forty to watch in the city of Pittsburgh by *Pittsburgh Magazine* for her important work in the area of inflicted childhood neurotrauma (shaken baby syndrome).

Army. This is a very special project targeting improved knowledge of the pathophysiology of blast-induced traumatic brain injury, and we are honored to participate. Second, Dr. Samuel Tisherman acquired funds to support a planned clinical trial for our novel emergency preservation and resuscitation (EPR) strategy. This trial will test the ability of EPR to save otherwise lethally wounded civilian victims of trauma and the support for this trial was acquired through a congressional appropriation and the Telecommunication Advanced Technology Research Center (TATRC) of the United States Army.

...we are continuing to grow and expand now in our 28th year of operation and my 12th year as Center director. Third, Dr. Rachel Berger was selected by *Pittsburgh Magazine* as one of the "Forty under Forty" to watch in the city of Pittsburgh based on her seminal work on the use of serum biomarkers to help pediatricians in making the diagnosis of inflicted childhood neurotrauma—more commonly known as the shaken baby syndrome. Fourth, among the many

accolades received by investigators and trainees at our center this academic year was a remarkable performance at the 2006 Congress of the Society of Critical Care Medicine (SCCM), where five Safar Center trainees received awards (please see the cover of this report), and where I was also fortunate to have received the 2006 Distinguished Investigator Award from the American College of Critical Care Medicine (ACCM). Details on these and a number of other grants and awards can be found later in this letter.

Dr. Patrick Kochanek received the 2006 Distinguished Investigator Award from the American College of Critical Care Medicine (ACCM) for his work in experimental and clinical traumatic brain injury. He was the 17th receipient of the award in the field and he was only the second Pediatrician to ever receive the award. CPR pioneer Dr. Safar also received the award in 1995. Pictured from left to right are Deborah Armstrong, PharmD, FCCM, from the ACCM and Patrick Kochanek, MD, FCCM.



NEW GRANTS

There were several new grants awarded to Safar

Center scientists. First, as mentioned in the introduction, many of the scientists in our center along with several of our key collaborators will participate in the PREVENT blast injury project funded by DARPA. This very special project targets the critical problem of blast-induced traumatic brain injury that most commonly results from improvised explosive devices (IEDs) used in terrorists attacks. Our investigative team joins principal investigator Dr. Richard Bauman at the Walter Reed Army Institute of Research and Steve Parks at ORA, along with teams from Harvard and Yale Schools of Medicine. Second, Dr. Samuel Tisherman will begin a multi-center clinical feasibility trial of our novel EPR strategy as a result of successfully acquiring funding from TATRC of the United States Army via a congressional appropriation. Dr. Lyn Yaffe, former director of research programs at the United States Naval Medical Research Institute was instrumental in facilitating acquisition of this support, and we thank him for his efforts on behalf of this novel and important project.

AWARDS & ACCOMPLISHMENTS OF TRAINEES & FACULTY

As previously mentioned, this year, Safar Center trainees received a remarkable five awards at the 2006 Congress of the SCCM. Specifically, senior Pediatric Critical Care Medicine fellow in the program at Children's Hospital of

Pittsburgh, Dr. Alia Dennis won the SCCM In-Training Award for her abstract titled: "Effect of hemorrhagic shock on cerebral blood flow in experimental traumatic brain injury: Magnetic resonance imaging assessment." The In-Training Award is given in recognition of the top abstract submitted by a fellow to the Congress. Also remarkable, University of Pittsburgh junior medical student M. Lee Haselkorn won one of the Scientific Awards for his abstract titled: "Effect of hemorrhagic shock on neuronal death after experimental traumatic brain injury in mice." Lee is a junior medical student at the University of Pittsburgh, who ultimately plans on doing a residency in Anesthesiology. Lee was part of the new Scholarly Project program that was recently put in place in the Medical School by Senior Vice Chancellor Dr. Arthur Levine.

At that same congress, Dr. Craig Smith, 2nd year Pediatric Critical Care Medicine fellow, won one of the Scientific Awards for his abstract titled: "Gender- and Cell Compartment-Dependent Poly-ADP-Ribosylation after Traumatic Brain Injury in Juvenile Rats," and Dr. Ajit Sarnaik, also a 2nd year Pediatric Critical Care Medicine fellow, won an Educational Scholarship for his abstract titled "The potential influence of ATP binding cassette subfamily B-1 polymorphisms in traumatic brain injury." Finally, PhD candidate Ava Puccio in the School of Nursing received the Nursing Section Award for her research in the area of oxidative stress and experimental traumatic brain injury." I am thrilled for these trainees, and I know that the many mentors involved in their development echo congratulations to these promising young scientists. I am pleased to report that Drs. Smith and Sarnaik will be funded by our T-32 training grant titled "Training in Pediatric Neurointensive Care and Resuscitation Research" beginning in July 2007.



Dr. Mioara Manole (right) received the 5th Nancy Caroline Fellow Award from Dr. Kochanek (left). The award is given to the top fellow at the Safar Center, as voted by the Associate Directors of the Center. On May 31, 2007 at the 5th Safar Symposium, at the University of Pittsburgh School of Medicine, Dr. Mioara Manole received the 5th Nancy Caroline Fellow Award. The award is made each year for the top fellow in training at the Safar Center and honors Dr. Nancy Caroline, who was one of the first fellows in our center and a pioneer in the development of the modern-day paramedic system through her work on the historic Freedom House Ambulance Service in the 1970s in the city of Pittsburgh. Dr. Manole is a Pediatric Emergency Medicine Fellow from Children's Hospital of Pittsburgh who is studying cerebral blood flow disturbances after experimental cardiac arrest in a project that is being carried out in collaboration with Dr. Chien Ho and his team at the Pittsburgh NMR Center for Biomedical Research, Carnegie Mellon University. Dr. Manole is in the first year of training on our aforementioned T32 grant from the National Institute of Child Health and Human Development.

A number of other trainees received grants or awards for their work at the Safar Center during the 2006/2007 academic year. Damian Clossin and Brett Postal were awarded the University of Pittsburgh Brackenridge Scholarship to participate in undergraduate research under the guidance of Safar Center Associate Director, Dr. Amy Wagner, in the Department of PM&R. Damian uses voltammetry to assess the effects of Methylphenidate on neurotransmission in experimental traumatic brain injury and Brett assesses cerebrospinal fluid biomarkers and their relationships to neurosteroids and outcome in adults with severe traumatic brain injury. Shaun Darrah, another undergraduate student, works with Dr. Wagner as part of a National Institute of Mental Health fellowship for undergraduate student research. Similarly, Laura Drewencki, a graduating senior at the University of Pittsburgh, was awarded the Bradler Award in Neuroscience. This award is given to students who have excelled academically and whose research experiences have shaped their future career plans. Laura will be attending medical school in the fall of 2007.

As mentioned in the introduction, Dr. Kochanek received the 2006 Distinguished Investigator Award from the ACCM, and gave the convocation address to the College. He was only the second University of Pittsburgh Faculty Member to receive the award. In May of 2007, Dr. Kochanek was also privileged to serve as the First Visiting Professor for the Center of Critical Illness and Health Engineering, at Washington University, St. Louis School of Medicine. Finally, on June 11-12, 2007, Drs. C. Edward Dixon and Patrick Kochanek participated in the stakeholder's meeting that was held in Baltimore, Maryland that focused on defining the research goals for research in the field of traumatic brain injury for the United States Army.



Safar Center Associate Director Dr. Amy Wagner and one of her students, Bradler Neuroscience Award Winner, Laura Drewencki were featured in an article in Pitt Magazine. Dr. Wagner is a role model in the field of Physical Medicine and Rehabilitation who enthusiastically and successfully mentors a large number of students interested in research.

SPECIAL EVENTS

On February 15, 2007 – as part of

African American History month, the University of Pittsburgh hosted the premiere, at the Twentieth Century Club, of a fantastic new documentary on the Freedom House Project. The Freedom House ambulance service, which was initiated and overseen in the late 1960s by Drs. Peter Safar and Nancy Caroline, served as the role model for the ultimate development of modern day emergency medicine services (EMS). The documentary was produced and directed by Gene Starzenski and gave a stirring portrayal of many of the first paramedics in the United States. We were very pleased to be able to participate in this event.

On May 31st, the 5th Safar Symposium, at the University of Pittsburgh, included a special focus during its morning program on blast-induced traumatic brain injury that included a number of renowned experts on the topic. More details on the Symposium and the 2007 Peter and Eva Safar Lecture for the Medical Sciences and Humanities is provided later in this report in a section devoted to these two linked events.



Announcement for the new documentary film on the Freedom House Ambulance project.



Dr. Peter Safar (2nd row, first on the left) and the participants in the Freedom House Ambulance project in Pittsburgh in 1975. This project was instrumental to the development of EMS world-wide. Project leader Dr. Nancy Caroline (1st row, center) was one of Dr. Safar's early fellows who went on to become the "Mother of EMS" and Director of the Red Cross in Israel.

GUEST PROFESSORS

This year, we hosted two guest

professors including Drs. Sten Rubertsson (see below) and David Meaney. On February 6, 2007, Dr. David Meaney, Professor, Dept.

of Bioengineering, University of Pennsylvania, Philadelphia, PA visited our center and discussed his important work in the area of in vitro models of experimental traumatic brain injury in a presentation titled "Targeting NMDA Receptors to Control Neuronal Fate after Traumatic Brain Injury." Dr. Meaney has been instrumental in assisting Drs. Hülya Bayır and Robert Clark in establishing an

Dr. Meaney has been instrumental in assisting Drs. Hülya Bayır & Robert Clark in establishing an in vitro stretch model of neuronal injury at the Safar Center.

in vitro stretch model of neuronal injury at the Safar Center. We are very grateful for his assistance in adding this new dimension to our Center.

In addition to the guest professors, we also hosted Dr. Lijun Yu, as a visiting scientist from China. Dr. Yu came to our Center as part of a visiting scientist program organized through the School of Medicine.

Dr. Rubertsson, a former fellow at the Safar Center and currently Professor of the Department of Surgical Sciences/ Anesthesiology and Intensive Care Uppsala University Hospital spoke on the successful application of mild therapeutic hypothermia in his center and also presented the 5th Annual CCM Distinguished Alumnus Lecturer for our Department. He and a number of clinical scientists in the Scandinavian countries have led the way in the implementation of therapeutic mild hypothermia in clinical care of adults with cardiopulmonary arrest.



ACKNOWLEDGEMENT I would like to

once again thank everyone working at the Center for a terrific job this year. I am indebted to Linda Ryan, 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*. I also thank Henry Alexander, John Melick, Keri Feldman, Vincent Vagni, Xiecheng Ma, 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. Thanks also to Tara Redwing for her help with fellow trainees.

I thank Drs. Ann Thompson, 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. Lina Du, John Williams, Milos Ikonomovic, Minke Tang, David Adelson, Dade Lunsford, Paul Paris, David Perlmutter, Hong Yan, Miro Klain, Steven Graham, Steven DeKosky, Glen Gobble, and Robert Hickey for their help. Special thanks to Dr. Ross Zafonte for his efforts in Newsome for their helpful veterinary support.

I also wish to acknowledge many outside collaborators who make critical contributions to our mission. These include Drs. Carleton Hsia and Li Ma, Synzyme of Technologies for important collaboration on our US Army funded work on novel resuscitation fluids, Drs. Richard Bauman and Joseph Long at the Walter Reed Army Institute for Research and Steve Parks from ORA for valuable discussions, and collaboration on the PREVENT program, Dr. Jurgen Schnermann at NIDDK and Dr. Jiang-Fan Chen at Boston University.

Many other individuals were helpful to our Center this year. I would also like to acknowledge Drs. Carol Nicholson, Ralph Nitkin, Beth Ansel, and Michael Weinrich of the National Center for Medical Rehabilitation Research, Dr. Ramona Hicks at the National Institute of Neurological Disorders and Stroke, Colonel Geoff Ling at DARPA, Colonel Robert Vandre, at the United States Army Medical Research and Materiel Command, Dr. Frank Tortella also at Walter Reed Army Institute for Research, and Mr. Robert Read at TATRC for their efforts on behalf of our Center and its investigators. Thanks are also in order for Dr. Lyn Yaffe, CEO of EPR Technologies, who continues to contribute enormously to

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."

helping closely link the PM&R Department with our Center. We will miss him as he moves to his new position at Harvard Medical School. I am especially thankful to Dr. Ann Thompson for her continued support and guidance. Dr. Thompson did a spectacular job as interim chairman of our Department.

I am also extremely grateful to a number of key collaborators in or affiliated with the University of Pittsburgh including Dr. Valerian Kagan at the University of Pittsburgh Center for Free Radical and Antioxidant Health, Dr. Edwin Jackson at the Center for Clinical Pharmacology, 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. Samuel Poloyac and Michael Tortorici in the School of Pharmacy, Dr. Simon Watkins in the Dept. of Cell Biology and Physiology, Drs. Yvette Conley and Sheila Alexander from the School of Nursing, Dr. Timothy Billiar in the Dept. of Surgery, Drs. Peter Wipf at the Combinatorial Chemistry Center and the Center for Chemical Methodologies and Library Development, and Joel Greenberger and Michael Epperly in the Dept. of Radiation Oncology. Expertise of these individuals greatly raises the level of the research at the Safar Center. Special thanks to Drs. Robert Wagner and Joseph our success. I also owe a debt of gratitude to Mr. Tore Laerdal of Laerdal Medical. His support, along with the support of the Laerdal Foundation, 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 Kristen Shaw 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 2007/2008 in our investigative efforts to develop new therapies in the field of resuscitation medicine, and thank you for your continued support of our work.

...LATE BREAKING NEWS..

As we go to press with this report, I am pleased to announce that Safar Center Associate Director, Dr. Hülya Bayır was awarded R21 and RO1 awards from the NIH. Dr. Bayır is also an Associate Director of Dr. Valerian Kagan's impressive Pittsburgh Center for Free Radical and Antioxidant Health, in the Department of Environmental and Occupational Health. Hülya has served as a wonderful link between these two Centers—melding state-of-the-art techniques in both free radical biology and experimental and clinical resuscitation medicine.



Dr. Hülya Bayır was awarded R21 and R01 grants from the NIH for her work on novel oxidative lipidomics applications in experimental cadiopulmonary arrest and clinical traumatic brain injury. Dr. Bayır is one of the emerging academic stars in the field of Pediatric Critical Care Medicine.

Also as we go to press with this report, our work with therapeutic hypothermia including both our EPR program and research on mild hypothermia is being featured in articles in the August 2007 issue of Science and in Forbes Magazine. More on these high profile publications in next year's report.

Dr. Hank Weiss has stepped down as director of the CDC-funded University of Pittsburgh Center for Injury Research and Control (CIRCL). I would like to personally thank Dr. Weiss for outstanding leadership of that project, which has been of great importance to our center and its mission. We look forward to working with Dr. P. David Adelson, who will take over as principal investigator of CIRCL.

Finally, we are pleased to be able to work with Dr. Derek Angus, the new chairman of the Department of Critical Care Medicine, in continuing to advance the research excellence of both the Safar Center and the Department of Critical Care Medicine. The Department of Critical Care Medicine continues to provide vital support to the Safar Center and its many missions.

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

SCIENTISTS

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

ASSOCIATE SCIENTISTS

Steven T. DeKosky, MD Lina Du. MD Ericka L. Fink, MD Lesley M. Foley, B.Sc. (Hon) Robert Garman, DVM Steven H. Graham, MD, PhD Melinda F. Hamilton, MD T. Kevin Hitchens, PhD Robert W. Hickey, MD Milos Ikonomovic, MD James J. Menegazzi, PhD Samuel M. 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

* Denotes current T32 fellow

FELLOWS

Jennifer Arnold, MD * Xiangbai Chen, MD, PhD Alia M. Dennis, MD Tomas Drabek, MD Mioara Manole, MD * Joelle Scanlon, PhD Karen Walson, MD

SUPPORT STAFF

Fran Mistrick Jackie Pantazes Marci Provins Emily Rogers Linda Ryan Julian Smith

Adib Abla Louis Archilla James W. Bales Lauren Bueke Joshua Burkhardt Amber Casey Damian Clossin J'Mir Cousar Ashley R. Crumbly Erin Cummings Shaun Darrah Julie Dobos Laura Drewencki Jesse Fisk Xiecheng Ma, MD Christina Marco John Melick Paula Nathaniel Jason Stezoski Vince Vagni STUDENTS Ashley Grosvenor Adam Olsen

Rashed Harun

Candace Hess

Lauren Kmec

Matt LaRosa

Evan Lebowitz

Pallavi Luthra

Megan Miller

Laura Mohler

George Nikhil

Rebecca Malena

Annie Hoffman

Ashley Kochanek

M. Lee Haselkorn

Larry W. Jenkins, PhD

Anthony E. Kline, PhD

Samuel A. Tisherman, MD

Amy K. Wagner, MD

Preservation and Resuscitation

Associate Director, Molecular Biology

Associate Director, Rehabilitation Research

Associate Director, Shock and Emergency

Associate Director, Rehabilitation Research

Adam Olsen Monisha Panda Brett Postal Zachary Repanshek Kathleen Sachse Lindsay Semler Samuel S. Shin Chris Sozda Chris Stangey Anne Su Matthew Tormenti Brian Westergom

TECHNICIANS

Henry Alexander

Yaming Chen

Jeffrey Cheng

Sherman Culver

Ashley Glumac

Jeremy Henchir

Keri Feldman

Youming Li

Raymond Griffith

10 Safar Center for Resuscitation Research



he 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 once again to the faculty for their funding successes. Also, not reflected yet in the graphs of the 2006 funding that are depicted here are several newly renewed and funded grants including our PREVENT award from DARPA and our Congressional support managed through TATRC. 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 eleven academic years. This represents direct and indirect costs and is shown for total, extramural, and intramural grant support, and has remained quite stable.

Extramural funding sources included the NIH, the United States Army, the Centers for Disease Control and Prevention, the Laerdal Foundation, the American Heart Association-National Affiliate, and other sources. Intramural support 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.





Specific Sources of Grant Support 2006/2007



During the 2006/2007 academic year, Safar Center investigators had a total of 29 active grants, all of which were extramural. The direct and indirect costs for the full award periods of these grants totaled \$21, 358, 158 and this is plotted above for the current and preceding eleven academic years.

n 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 200,000 are hospitalized each year as a result of TBI, at an annual cost of about \$10 billion dollars for acute care and rehabilitation. Current treatment is comprised of supportive care and the control of brain swelling with resultant raised intracranial pressure. New therapies are badly needed.

and have been carrying out pioneering work that is explaining the link between oxidative stress and neuronal death after TBI. Their work has revealed that the mitochondrial lipid, cardiolipin is a critical early target for oxidative stress in the initial minutes to hours after injury. And this cardiolipin oxidation ultimately leads to release of cytochrome c into the cytoplasm of neurons with resultant triggering of neuronal death by apoptosis.

Safar Center investigators are in pursuit of new neuroprotective therapies that will improve the outcome of both adult and pediatric patients with TBI tackling this problem with strategies targeting from the field through to rehabilitation.

We are pleased to have program project grants from both the National Institutes of Health and the United States Army, along with participation in the PREVENT blast program funded by DARPA. More information on our Department of Defense-related work on TBI can be found in the section on Combat Casualty Care later in this report. Our investigators are also supported by a number of individual RO1 and R21 grants from the NIH.

Safar Center investigators working in the field of TBI are studying a number of promising pathways involved in the evolution of secondary damage after the initial impact—with a particular focus on the potential therapeutic targets after severe brain injury. Safar Center scientists have a remarkable 27 manuscripts published or in press from work on TBI during this academic year. A few highlights of this work are discussed below.

One of most exciting areas of investigation in TBI at the Safar Center relates to the work of Drs. Hülya Bayır and Valerian Kagan who are applying novel and unique oxidative lipidomics methods to experimental and clinical TBI samples, Related to this work, Dr. Bayır published an important paper in 2007 that demonstrated early and selective cardiolipin oxidation in the rat brain–using an experimental model of TBI that mimicked brain trauma in a young child. Her work was just published in the Annals of Neurology.

In a second active area of investigation in TBI, University of Pittsburgh MD, PhD student James Bales is working with Safar Center Associate Director Dr. C. Edward Dixon on the interaction between dopamine and adenosine receptors in the injured brain. His work under the mentorship of Dr. C. Edward Dixon typifies how investigators are using models of TBI that have been traditionally used to study the acute phase after injury, to identify more chronic pathophysiology. This approach has emerged in our Center through the linking of resuscitation and rehabilitation medicine. The relevance of this type of approach to the development of new therapies used in rehabilitation cannot be understated. For example, given the fact that A2a receptor antagonists are in clinical testing for Parkinson's disease, they might also have utility in the delayed rehabilitation phase after TBI or other acute brain injuries in humans.



MD, PhD student James Bales has demonstrated delayed up-regulation of adenosine A2a receptors in the striatum after experimental TBI - in studies targeting development of new treatments for the chronic phase after TBI in humans.



Drs. Hülya Bayır and Valerian Kagan are "re-writing the textbooks" by demonstrating the highly selective nature of oxidative damage that begins in the mitochondria after brain injury (see above figure). This contrasts the traditional random nature of oxidative damage that is generally described in reviews and chapters on oxidative stress and oxidative damage in acute brain injury. Based on the new knowledge that they have generated, Drs. Bayır and Kagan are targeting oxidative stress in mitochondria early after TBI in their current experiments. This could lead to a new breakthrough acute therapy for TBI in adults and children.

FACULTY

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 Lina Du, MD Weimin Gao, PhD Steven H. Graham, MD, PhD Larry W. Jenkins, PhD Anthony E. Kline, PhD Amy K. Wagner, MD Hong Yan, MD ardiac arrest in adults and children is an enormous public health problem. There are an estimated 330,000 out-ofhospital cardiac deaths per year in the United States. Overall survival rates from out-of-hospital cardiac arrests are estimated to be as low as 6% in both adults and children. Resuscitation leads to return of spontaneous circulation in less than 40% of arrest victims and traditionally only about 10% ever regain consciousness.

CARDIAC ARREST & **RESUSCITATION IN ADULTS**

Therapeutic hypothermia-a treatment that was pioneered in part by Safar Center investigators-is beginning to have an impact in reducing mortality and morbidity from cardiac arrest. At UPMC, greater than 85% of cardiac arrest victims who exhibit return of spontaneous circulation now receive therapeutic hypothermia and neurological outcomes of patients from this heretofore refractory condition are -for the first time-improving.

Therapeutic hypothermia - a treatment that was pioneered in part by Safar Center investigators - is beginning to have an impact in reducing mortality and morbidity from cardiac arrest.

Safar Center investigators published 15 papers on their original research in the area of cardiac arrest, in both laboratory and clinical work, and this included studies in the pediatric arena. These studies were funded by the NIH, the American Heart Association, and the Laerdal Foundation. Among the many highlights, Mike Tortorici published a comprehensive review article on the effect of mild hypothermia on drug metabolism in experimental and clinical cardiac arrest, in the journal Critical Care Medicine. That work was part of the thesis requirement for his PhD work, carried out under the mentorship of Dr. Samuel Poloyac in the School of Pharmacy. Drs. Poloyac and Callaway are now collaborating to study the effect of mild therapeutic hypothermia on drug metabolism in normal volunteers. These studies are important in that current pharmacotherapy in critical care of patients suffering cardiac arrest is not routinely adjusted for the use of mild hypothermia—which is known to alter drug metabolism. Given the increasing use of mild hypothermia, it will be essential to understand its impact on other therapies—in order to optimize its benefit.



Dr. Clifton Callaway, Associate Director of the Safar Center and Director of the Cardiac Arrest Program has begun to implement a University of Pittsburgh Medical Center system-wide effort to implement therapeutic hypothermia - based on the most recent guidelines of the American Heart Association.

CARDIOPULMONARY ARREST **IN INFANTS & CHILDREN**

Associate Directors Drs. Robert Clark and Hülya Bayır, along with new faculty member

Dr. Ericka Fink and T32 fellow Dr. Mioara Manole, are working to better understand the pathophysiology of cardiac arrest in children and to develop new treatments. In novel research in this area, Dr. Manole, under the mentorship of Dr. Clark, is pursuing therapies targeting cerebral blood flow promotion after cardiac arrest, while Dr. Bayır is evaluating both new anti-oxidant and anti-inflammatory therapies.

Dr. Ericka Fink was awarded a K12 grant from the National Institutes of Child Health and Human Development (NICHD) as part of the Pediatric Critical Care Scientist Development Program. This is a highly successful program initiated by Dr. Carol Nicholson at NICHD and overseen by Dr. J. Michael Dean at the Primary Children's Hospital in Salt Lake City that is targeted to aid in the development of clinician scientists in the field of pediatric critical care medicine. Dr. Fink graduated from our T32 training program. Her most recent studies are focused on the use of mild therapeutic hypothermia-translating her initial work in laboratory models to the bedside in the ICU at Children's Hospital of Pittsburgh.





Dr. Mioara Manole (seated on the right), was one of the award winners for her work on perfusion magnetic resonance imaging assessment of cerebral blood flow in a pediatric model of cardiac arrest at the Annual Fellow's Research Day, held in Pittsburgh by the American Heart Association. Dr. Manole's innovative work suggests that further improving blood flow may represent a new therapeutic avenue in the treatment of cardiac arrest in infants and children.

FACULTY

Clifton Callaway, MD, PhD Hülya Bayır, MD Robert W. Hickey, MD Samuel M. Poloyac, PharmD, PhD Samuel A. Tisherman, MD James J. Menegazzi, PhD

Robert S.B. Clark, MD Ericka L. Fink, MD Patrick M. Kochanek, MD Lina Du, MD

nflicted childhood neurotrauma remains the most important type of injury resulting from child abuse and the most common form of severe TBI in children less than two years of age. Commonly known as the shaken baby syndrome, this

form of TBI is the leading cause of death from trauma in infants. Approximately 1 in 3,300 infants less than 1 year of age are victims of severe or fatal inflicted childhood neurotrauma each year in the United States, and the number of more mild cases may be over 100 times greater. Recognition of this condition can be difficult for physicians.

Dr. Rachel Berger, Associate Director of the Safar Center and Director of the

This year, Dr. Rachel Berger and colleagues published a manuscript that revealved unique serum biomarker fingerprints in TBI, cardiac arrest and inflicted childhood neurotrama...

Child Abuse Program, is leading a team of collaborative investigators working toward the goal of developing a blood test to aid clinicians in making this difficult diagnosis, in studies funded by the Centers for Disease Control and Prevention (CDC), and the NIH. She has built upon the early biomarker work initiated by Dr. Kochanek and others at the Safar Center and has carried out a number of clinical trials that have greatly advanced the potential use of serum biomarkers in pediatric brain injury.



In January 2007, Safar Center investigators spearheaded publication of a special issue in the *Journal of Neurotrauma* focused on the topic of inflicted childhood neurotrauma. Three of the four co-editors of that issue, Drs. Patrick Kochanek, Rachel Berger, and Larry Jenkins, are Safar Center faculty. Dr. Susan Margulies from the University of Pennsylvania also was a co-editor. It was the first issue of that journal ever devoted to that important topic. The cover of that special issue is shown above. This year, Dr. Rachel Berger and colleagues published a manuscript that revealed unique serum biomarker fingerprints in TBI, cardiac arrest and inflicted childhood neurotrauma that may help clinicians better understand how injury to the brain evolves in these three important forms of pediatric brain injury. Her work published in the journal *Developmental Neuroscience* suggests that inflicted childhood neurotrauma exhibits a unique brain injury pattern that may be more amenable to delayed treatment than conventional TBI.

Seven papers in the area of child abuse research were authored by Safar Center investigators, including two manuscripts in the special issue of the *Journal of Neurotrauma*. In that issue, Drs. Weimin Gao and Larry Jenkins carried out the first proteomic assessment of cerebrospinal fluid (CSF) in victims of the shaken baby syndrome. Their studies suggested that potential delay in presentation or chronic injury in these infants is reflected in the CSF proteomic biomarker profile that is observed. This approach may ultimately help clinicians to better understand the evolution of brain damage in this important public health problem.

FACULTY

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 espite the millions of lives saved through the pioneering development and implementation of CPR by the late Dr. Peter Safar and its world-wide implementation facilitated by the development of the Resusci-Anne manikin by Mr. Asmund Laerdal and Dr. Bjorn Lind, many challenges remain in the field of resuscitation. One important insult that continues to have nearly 100 percent mortality in both the civilian and military settings is exsanguination cardiac arrest. This condition, which generally results from trauma, is not only a leading cause of

One important insult that continues to have nearly 100% mortality in both the civilian and military settings is exsanguination cardiac arrest. death of potentially salvageable combat casualties, but is also an important cause of death in civilian trauma.

In 1984 Dr. Safar with advice from Colonel Ronald Bellamy, an 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. EPR involves the use of a rapid ice-cold aortic flush to produce profound hypothermia (<10°C) and induce a preservation state in injury victims that "buys time" for the trauma surgeon to perform damage control surgery that is followed by a delayed resuscitation using cardiopulmonary bypass.

In the laboratory, Dr. Tomas Drabek, recipient of the Charles Schertz Fellow Award in 2007-2008 from the Department of Anesthesiology, published a manuscript on the development of a new rat model of EPR in the journal *Critical Care Medicine*. He developed this new model in rats to allow for testing of therapeutic adjuncts to cold flush, and to evaluate alternative flush solutions. Dr. Drabek is also using a variant of this approach to study deep hypothermia circulatory arrest, as it is currently used in cardiac surgery and has published a manuscript on this approach in *Life Sciences*.



Studies at the Safar Center have taken the concept of lifesaving emergency preservation from theory to reality. This year, Dr. Samuel Tisherman was funded via U.S. Congressional support to lead the first clinical feasibility trial of EPR. That trial will test whether EPR can save the lives of otherwise lethally injured civilians who are victims of exsanguination cardiac arrest. EPR has shown breakthrough potential in the laboratory and has generated a great deal of excitement among trauma surgeons at a number of major trauma centers in the United States.

FACULTY

Samuel A. Tisherman, MD Patrick M. Kochanek, MD S. William Stezoski Miroslav Klain, MD, PhD emorrhagic 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.

A number of therapies have been evaluated in experimental models of hemorrhagic shock at the Safar Center in order to improve outcomes of patients suffering hemorrhagic shock. Promising therapies in this regard have included mild hypothermia and intraperitoneal adenosine, among others (please see the 2005/2006 Annual Report at www.Safar.Pitt.edu).

This year, Dr. Rainer Kentner published a study in the journal *Resuscitation* that represented his final work during his tenure as a fellow at the Safar Center (January 1999 – December 2000). Dr. Kentner evaluated the antioxidant Tempol, and demonstrated that in the setting of uncontrolled hemorrhagic shock, the use of antioxidants can be potentially detrimental when combined with small volume resuscitation. One theory that may help explain this finding is that free radical production (i.e., superoxide anion) in the vasculature produces vasoconstriction, which–when prevented by antioxidants such as Tempol—may lead to a failure of compensatory vasoconstriction and exacerbate hypotension. This suggests that antioxidants may need to be combined with colloids or artificial hemoglobin molecules.

This year at the Safar Center, much of the research in the area of hemorrhagic shock was carried out in the area of combined TBI plus hemorrhagic shock, in a newly developed mouse model. That model was created to test novel therapies for the important terrorism-related problem of blast-TBI and blast-induced polytrauma. Additional discussion of that area of research can be found in this report in the section on "Combat Casualty Care."

FACULTY

Samuel A. Tisherman, MD Patrick M. Kochanek, MD nclusion 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 and is allowing Safar Center scientists to evaluate new treatments along the entire continuum of care of brain injury victims—from the field to rehabilitation.

In addition to the many studies of acute interventions for cerebral resuscitation that are being carried out at the Safar Center, our scientists are also evaluating the efficacy of rehabilitation-relevant therapies in the sub-acute and delayed periods after brain injury.

This year, Safar Center investigators working under the direction of Drs. Anthony Kline and Amy Wagner in the Department of PM&R published eight manuscripts in the arena of TBI rehabilitation.

Among the many other areas of study in this program, Dr. Amy Wagner is investigating how the hormonal response to TBI differs in male and female patients using CSF samples from patients with severe injuries that have been collected with the University of Pittsburgh Brain Trauma Research Center. There have been a number of studies in experimental models of brain injury that have identified important gender-related effects, few studies have attempted to bridge bench and bedside in this area. Dr. Wagner's CDC-funded research in this area hopes to identify how we can best tailor therapies based on genderdependent differences in the evolution of damage and repair in the injured brain.



Investigators in the rehabilitation program laboratory of Dr. Anthony Kline, from left to right Annie Hoffman, Anthony Kline, and Jeff Cheng. Research this year in the laboratory of Dr. Anthony Kline demonstrated that chronic administration of sedatives such as haloperidol can have profoundly deleterious effects on long-term recovery in experimental models of TBI. His work is of great importance because he is testing commonly used sedatives in the intensive care unit and showing that these agents may have deleterious long-term consequences. Much of the current use of sedative and analgesic agents in the critical care of patients with brain injury is empiric. Improved knowledge of the effects of these agents on brain recovery could favorably alter supportive care and improve outcomes.

FACULTY

C. Edward Dixon, PhD Anthony E. Kline, PhD Amy K. Wagner, MD here 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.

Combat-casualty care-related research at the Safar Center included work on two linked programs, that are focused on the problem of blast-induced TBI, namely 1) a US Army funded program to study novel resuscitation solutions in combat TBI and hemorrhagic shock and 2) participation in the new DARPA PREVENT blast program. Blast injury has become critically important in combat casualty care in light of the emergence of terrorist attacks using IEDs, and this problem may take on greater importance in the civilian sector as seen in events such as the Madrid bombing. Blast injuries that require resuscitation are complex and typically involve multiple simultaneous injuries such as TBI, orthopedic and soft tissue injury, eye injury, and burns. The use of body armor by our troops frequently protects the other vital organs; however, the shock states produced by these insults can lead to secondary damage.

A key goal this year was to develop a model of combined TBI plus hemorrhagic shock to mimic the commonly observed polytrauma that is seen after blast injury. In research funded by the United States Army, pediatric critical care medicine fellow Dr. Alia Dennis, working under the direction of Dr. Kochanek established a new mouse model of combined TBI plus hemorrhagic shock. This model can be used to test both new resuscitation fluids and novel therapies. For her work, Dr. Dennis received the In-Training Award (see cover photo of this annual report) award, for the top paper by a trainee presented at the annual Congress of the Society of Critical Care Medicine.

In collaboration with Drs. Carleton Hsia and Li Ma at Synzyme Technologies, we are testing two novel resuscitation solutions including polynitroxyl albumin (PNA) and polynitroxyl pegylated hemoglobin (PNPH) in this combined injury model—comparing them to the standard approaches used in both combat casualty care and civilian trauma. We are seeking an approach that yields a small volume resuscitation fluid which can be easily carried by a military medic, promptly restores blood pressure to optimize cerebral perfusion, while minimizing the development of brain swelling, secondary damage, and any deleterious consequences of PNH hemoglobin.

In the proposed work within the DARPA-funded research, Dr. Kochanek, along with a team of talented scientists at the Safar Center and collaborators including Co-PI Drs. Larry Jenkins, Hülya Bayır, Robert Clark, C. Edward Dixon, Robert Garman, Edwin Jackson, and Valerian Kagan will define the neuropathology and biochemical and molecular derangements in the injured brain that are associated with experimental blast-induced TBI. Safar Center investigators are collaborating with Drs. Richard Bauman and Joseph Long at Walter Reed Army Institute for Research, Steve Parks at ORA, and investigative teams at both the Harvard and Yale Schools of Medicine to tackle this vital research area.

A key goal this year was to develop a model of combined TBI plus hemorrhagic shock to mimic the commonly observed polytrauma that is seen after blast injury.

Blast-induced brain injury

Traumatic brain injury accounts for nearly 60 percent of all injuries among U.S. troops. A subset includes blast-induced injuries that could cause serious problems, even if shrapnel from the explosion never hits the soldier.



TRIBUNE-REVIEW

On May 31, 2007 The Pittsburgh Tribune-Review featured an article titled "Shock wave injuries top Pitt symposium" which discussed the critical problem of blast-induced TBI, and discussed the research of the newly funded PREVENT blast program by DARPA in which the Safar Center is participating. This special program hopes to provide a better understanding of the pathophysiology of blast-induced TBI along with the development of both preventative and therapeutic measures.

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

he 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.

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. We are pleased that a "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, and encourage prospective candidates to apply.

Annie Hoffman, working under the mentorship of Dr. Anthony E. Kline during the 2006/2007 academic year, received a travel fellowship to attend and present her undergraduate honors research at the 2007 Society for Neuroscience meeting in San Diego, CA.

In the last 7 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. As outlined in the introductory letter of this report, Dr. Hülya Bayır just received her first RO1 award from the NIH. This is a fabulous accomplishment by Dr. Bayır, a Pediatric Critical Care Medicine Clinician-Scientist who—early in her career—was jointly mentored by both Dr. Valerian Kagan at the Pittsburgh Center for Free Radical and Antioxidant Health and Dr. Kochanek at the Safar Center. Dr. Bayır represents a perfect example of how dual mentorship between collaborating scientists and faculty at the Safar Center can produce a complimentary environment that fosters the development of young investigators—and ultimately, creates superb faculty members.

Hülya Bayır, MD Michael J. Bell, MD Rachel P. Berger, MD, MPH Ericka L. 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

The Safar Center 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.

Many students also made important discoveries in research under the guidance of Safar Center scientists this year. Two special accomplishments by students this year at our Center were achieved by University of Pittsburgh Undergraduate Annie Hoffman, and Pitt Medical student M. Lee Haselkorn.

Annie Hoffman, working under the mentorship of Dr. Anthony E. Kline during the 2006/2007 academic year, received a travel fellowship to attend and present her undergraduate honors research at the 2007 Society for Neuroscience meeting in San Diego, CA. She was 1 of 15 students nationally to receive this award from the Faculty for Undergraduate Neuroscience.

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



Pitt Medical Student M. Lee Haselkorn (right), working with Drs. Kochanek (center) and Alia Dennis (left) as part of the Senior Vice Chancellor's new "Scholarly Project" program, received one of the Scientific Awards at the 2006 Congress of the SCCM for his work on the neuropathology of combined TBI and hemorrhagic shock in mice. Lee also was recognized by the University of Pittsburgh School of Medicine for this research.

n May 31, 2007, David M. Gaba, MD, Associate Dean for Immersive and Simulation-based Learning and Professor of Anesthesia at Stanford University School of Medicine served as the 27th Peter and Eva Safar Lecturer in Medical Sciences and Humanities. Dr. Gaba directs the Patient Safety Culture Institute and the Patient Simulation Center of Innovation at Veterans Affairs Palo Alto Health Care System where he is a Staff Anesthesiologist. Over the last 22 years his laboratory has pioneered applying organizational safety theory to health care. He and his team invented the modern full-body patient simulator and is responsible for introducing Crew Resource Management training from aviation to healthcare, first in anesthesia and then to many other healthcare domains. He has been the principal investigator on grants from a wide variety of funding organizations, and is the PI on projects concerning safety culture in hospitals and on applying simulation to address safety culture in diverse types of hospitals ranging from rural critical access hospitals to large urban academic centers. Dr. Gaba authored more than 75 original articles and editorials in a wide spectrum of journals, along with 18 book chapters, and one influential book: Crisis Management in Anesthesiology (which has been translated into three other languages). He is a founding member of the Research Committee of the National Patient Safety. He is a current and founding board member of both the Society for Simulation in Healthcare and the Advanced Initiatives on Medical Simulation, and a founding member of the Committee on Simulation of the American Society of Anesthesiologists. Dr. Gaba is the current and founding Editor-in-Chief of the journal Simulation in Healthcare, the only peer-reviewed journal on simulation, published by the Society for Simulation in Healthcare. Many of Dr. Gaba's fellows, faculty collaborators, and protégés have gone on to leadership positions on human performance in healthcare, organizational safety, and simulation in healthcare throughout the world.



Dr. David Gaba, Associate Dean for Immersive and Simulation-based Learning and Professor of Anesthesia at Stanford University School of Medicine served as the 27th Peter and Eva Safar Lecturer in Medical Sciences and Humanities.



From left to right: Dr. John Williams, Dr. David Gaba, Mrs. Eva Safar, and Dr. Patrick Kochanek at the 27th Peter and Eva Safar Lecture.



Col. Geoff Ling gave a stirring presentation about the problems of blast-induced TBI in the Iraq War.

n May 31, 2007, the Safar Center hosted the 5th 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. This year's recipient was Dr. Mioara Manole (please see introductory letter of this report).

The morning session on "Advances in Resuscitation Medicine" focused on "Blast-Induced TBI" and featured a stirring opening presentation on the current problem in Operation Iraqi Freedom by COL Geoff Ling, MD, PhD, Program Manager, DARPA, titled "Blast-Induced Traumatic Brain Injury: An Overview of an Emerging Problem in Military Trauma and Terrorism;" and an important presentation by combat casualty neurosurgeon COL James M. Ecklund, MD, FACS, on "Blast-Induced Traumatic Brain Injury: Clinical Perspective from the Iraq War." In addition, Dr. Faris A. Bandak, PhD, Professor of Neurology, F. Edward Hébert School of Medicine, Uniformed Services University of the Health Sciences, presented recent data on "Computational Biomechanics in Blast Neurotrauma;" Richard Bauman, PhD, Systems Integrator, DARPA and Joseph Long, PhD, Chief, Department of Polytrauma and Resuscitation Research, Division of Military Casualty Research at

Walter Reed Army Institute for Research, spoke about "Rodent Models of Blast-Induced Traumatic Brain Injury;" and Steven A. Parks, Commander USN (ret) and President, ORA, presented his work on "Recent Developments in Large Animal Modeling of Blast-Induced Traumatic Brain Injury." The morning session concluded with a presentation by Safar Center fellow, Dr. Alia Dennis about her work on "Combined Traumatic Brain Injury and Hemorrhagic Shock in Mice: A New Model and Novel Assessment by Perfusion Magnetic Resonance Imaging." The morning session was exceptional and important to the ongoing research at the Safar Center.

Speakers at the afternoon session focused on "Advances in Human Simulation Education" and included Dr. Mark Bowyer, COL, USAF, MC, and Chief, Division of Trauma and Combat Surgery, Uniformed Services University, who gave a fascinating presentation on "Surgical Simulation: The Current and Near Future Promise;" William McGaghie, PhD, Professor, Medical Education and Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, who presented on "Advances in Simulation-Based Medical Education and Research;" Dr. Amitai Ziv, MD, MHA, Deputy Director, Sheba Medical Center, Tel Hashomer, Israel, Founder and Director, MSR – The Israel Center for Medical Simulation, who presented on "Simulation-Based Education on a National Scale: The Israeli Experience;" Elizabeth Hunt, MD, MPH, Director, Johns Hopkins Simulation Center, who presented on "The Use of Simulation in Pediatrics to Improve Quality of Care;" and concluded with Amy Seybert, PharmD, Assistant Professor of Pharmacy and Therapeutics, University of Pittsburgh School of Pharmacy and Pharmaceutical Care Coordinator, Critical Care, University of Pittsburgh Medical Center, who discussed "Simulation-Based Learning in Pharmacy Education." This was the first year that the afternoon session was held at WISER, which was a spectacular venue and greatly facilitated audience participation and discussion.

The symposium was attended by over 120 participants. We are grateful to DARPA, the Laerdal Foundation, the United States Army TATRC and the USAMRMC 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. We are thankful to all supporters of this symposium.

The afternoon session of the Symposium at WISER was appreciated by a large and enthusiastic audience.



PEER-REVIEWED MANUSCRIPTS

- Baserga M, Hale MA, Ke X, Wang ZM, Yu X, Callaway CW, McKnight RA, Lane RH: Uteroplacental insufficiency increases p53 phosphoyrylation without triggering the p53-MDM2 functional circuit response in the IUGR rat kidney. Am J Physiol Regul Integr Comp Physiol 292:R1943-1955, 2007.
- 2. Basova LV, Kurnikov IV, Wang L, Ritov VB, Belikova NA, Vlasova II, Pacheco AA, Winnica DE, Peterson J, Bayir H, Waldeck DH, Kagan VE: Cardiolipin switch in mitochondria: shutting off the reduction of cytochrome c and turning on the peroxidase activity. Biochemistry 46:3423-3434, 2007.
- 3. Bayır H, Kochanek PM, Kagan VE: Oxidative stress in immature brain after traumatic brain injury. Dev Neurosci 28:420-431, 2006.
- Bayır H, Kagan VE, Clark RS, Janesko-Feldman K, Rafikov R, Huang Z, Zhang X, Vagni V, Billiar TR, Kochanek PM: Neuronal NOS-mediated nitration and inactivation of manganese superoxide dismutase in brain after experimental and human brain injury. J Neurochem 101:168-181, 2007.
- 5. Bayır H, Tyurin VA, Tyurina YY, Viner R, Ritov V, Amoscato AA, Zhao Q, Zhang XJ, Janesko-Feldman KL, Alexander H, Basova LV, Clark RS, Kochanek PM, Kagan VE: Selective early cardiolipin peroxidation after traumatic brain injury: an oxidative lipidomics analysis. Ann Neurol (in press).
- 6. Beers SR, Berger RP, Adelson PD: Neurocognitive outcome and serum biomarkers in inflicted versus non-inflicted traumatic brain injury in young children. J Neurotrauma 24:97-105, 2007.
- 7. Berger RP: The use of serum biomarkers to predict outcome after traumatic brain injury in adults and children. J Head Trauma Rehabil 21:315-333, 2006.
- 8. Berger RP, Adelson PD, Richichi R, Kochanek PM: Serum biomarkers after traumatic and hypoxemic brain injuries: insight into the biochemical response of the pediatric brain to inflicted brain injury. Dev Neurosci 28:327-335, 2006.
- 9. Betz AE, Menegazzi JJ, Logue ES, Callaway CW, Wang HE: A randomized comparison of manual, mechanical and highimpulse chest compression in a porcine model of prolonged ventricular fibrillation. Resuscitation 69:495-501, 2006.
- 10. Callaway CW, Hostler D, Doshi AA, Pinchalk M, Roth RN, Lubin J, Newman DH, Kelly LJ: Usefulness of vasopressin administered with epinephrine during out-of-hospital cardiac arrest. Am J Cardiol 98:1316-1321, 2006.
- 11. Cao G, Xing J, Xiao X, Liou AK, Gao Y, Yin XM, Clark RS, Graham SH, Chen J: Critical role of calpain I in mitochondrial release of apoptosis-inducing factor in ischemic neuronal injury. J Neurosci (in press).
- Cheng JP, Aslam HA, Hoffman AN, Zafonte RD, Kline AE: The neurobehavioral benefit conferred by a single systemic administration of 8-OH-DPAT after brain trauma is confined to a narrow therapeutic window. Neurosci Lett 416:165-168, 2007.
- 13. Clark RS, Vagni VA, Nathaniel PD, Jenkins LW, Dixon CE, Szabo C: Local administration of the Poly(ADP-Ribose) polymerase inhibitor INO-1001 prevents NAD(+) depletion and improves water maze performance after traumatic brain injury in mice. J Neurotrauma (in press).
- Clark RS, Nathaniel PD, Zhang X, Dixon CE, Alber SM, Watkins SC, Melick JA, Kochanek PM, Graham SH: boc-Aspartyl(OMe)-fluoromethylketone attenuates mitochondrial release of cytochrome c and delays brain tissue loss after traumatic brain injury in rats. J Cereb Blood Flow Metab 27:316-326, 2007.
- 15. Cousar JL, Lai Y, Marco CD, Bayır H, Adelson PD, Janesko-Feldman KL, Kochanek PM, Clark RS: Heme oxygenase 1 in cerebrospinal fluid from infants and children after severe traumatic brain injury. Dev Neurosci 28:342-347, 2006.
- DeKosky ST, Abrahamson EE, Ciallella JR, Paljug WR, Wisniewski SR, Clark RS, Ikonomovic MD: Association of increased cortical soluble abeta42 levels with diffuse plaques after severe brain injury in humans. Arch Neurol 64:541-544, 2007.
- Drabek T, Fisk JA, Dixon CE, Garman RH, Stezoski J, Wisnewski SR, Wu X, Tisherman SA, Kochanek PM: Prolonged deep hypothermic circulatory arrest in rats can be achieved without cognitive deficits. Life Sci 2007 Jun 29; [Epub ahead of print].

- Drabek T, Stezoski J, Garman RH, Wu X, Tisherman SA, Stezoski SW, Fisk JA, Jenkins L, Kochanek PM: Emergency preservation and delayed resuscitation allows normal recovery after exsanguination cardiac arrest in rats: a feasibility trial. Crit Care Med. 35:532-537, 2007.
- 19. Fu Q, McKnight RA, Yu X, Callaway CW, Lane RH: Growth retardation alters the epigenetic characteristics of hepatic dual specificity phosphatase 5. FASEB J 20:2127-2129, 2006.
- Gao WM, Chadha MS, Berger RP, Omenn GS, Allen DL, Pisano M, Adelson PD, Clark RS, Jenkins LW, Kochanek PM: A gel-based proteomic comparison of human cerebrospinal fluid between inflicted and non-inflicted pediatric traumatic brain injury. J Neurotrauma 24:43-53, 2007.
- 21. Ho Y, Logue E, Callaway CW, DeFranco DB: Different mechanisms account for extracellular-signal regulated kinase activation in distinct brain regions following global ischemia and reperfusion. Neuroscience 145:248-255, 2007.
- 22. Hostler D, Callaway CW, Newman DH, D'Cruz B: Thrombin-antithrombin appearance in out-of-hospital cardiac arrest. Prehosp Emerg Care 11:9-13, 2007.
- 23. Hostler D, Rittenberger JC, Roth R, Callaway CW: Increased chest compression to ventilation ratio improves delivery of CPR. Resuscitation (in press).
- 24. Targeting nitroxides to mitochondria: location, location, location, and...concentration: highlight commentary on "Mitochondria superoxide dismutase mimetic inhibits peroxide-induced oxidative damage and apoptosis: role of mitochondrial superoxide. Free Radic Biol Med 2007 Apr 1; [Epub ahead of print].
- 25. Kagan VE, Tyurina YY, Bayır H, Chu CT, Kapralov AA, Vlasova II, Belikova NA, Tyurin VA, Amoscato A, Epperly M, Greenberger J, Dekosky S, Shvedova AA, Jiang J: The "pro-apoptotic genies" get out of mitochondria: oxidative lipidomics and redox activity of cytochrome c/cardiolipin complexes. Chem Biol Interact 163:15-28, 2006.
- 26. Kentner R, Safar P, Behringer W, Wu X, Henchir J, Ma L, Hsia CJ, Tisherman SA: Small volume resuscitation with tempol is detrimental during uncontrolled hemorrhagic shock in rats. Resuscitation 72:295-305, 2007.
- 27. Kline AE, Massucci JL, Zafonte RD, Dixon CE, DeFeo JR, Rogers EH: Differential effects of single versus multiple administrations of haloperidol and risperidone on functional outcome after experimental brain trauma. Crit Care Med 35:919-924, 2007.
- 28. Kline AE, Wagner AK, Westergom BP, Malena RR, Zafonte RD, Olsen AS, Sozda CN, Luthra P, Panda M, Cheng JP, Aslam HA: Acute treatment with the 5-HT(1A) receptor agonist 8-OH-DPAT and chronic environmental enrichment confer neurobehavioral benefit after experimental brain trauma. Behav Brain Res 177:186-94, 2007.
- Kochanek AR, Kline AE, Gao WM, Chadha M, Lai Y, Clark RS, Dixon CE, Jenkins LW: Gel-based hippocampal proteomic analysis 2 weeks following traumatic brain injury to immature rats using controlled cortical impact. Dev Neurosci 28:410-419, 2006.
- Lai Y, Stange C, Wisniewski SR, Adelson PD, Janesko-Feldman KL, Brown DS, Kochanek PM, Clark RS: Mitochondrial heat shock protein 60 is increased in cerebrospinal fluid following pediatric traumatic brain injury. Dev Neurosci 28:336-341, 2006.
- 31. Lo BM, Quinn SM, Hostler D, Callaway CW: Rescue shock outcomes during out-of-hospital cardiac arrest. Resuscitation (in press).
- 32. Logue ES, McMichael MJ, Callaway CW: Comparison of the effects of hypothermia at 33 degrees C or 35 degrees C after cardiac arrest in rats. Acad Emerg Med 14:293-300, 2007.
- 33. Mader TJ, Menegazzi JJ Betz AE, Logue ES, Callaway CW, Sherman LD: Adenosine A1 receptor antagonism hastens the decay in ventricular fibrillation waveform morphology during porcine cardiac arrest. Resuscitation 71:254-259, 2006.
- 34. Manole MD, Hickey RW, Momoi N, Tobita K, Tinney JP, Suciu GP, Johnnides MJ, Clark RS, Keller BB: Preterminal gasping during hypoxic cardiac arrest increases cardiac function in immature rats. Pediatr Res 60:174-179, 2006.

- 35. Nemoto EM, Rao G, Robinson T, Saunders T, Kirkman J, Davis D, Kuwabara H, Dixon CE: Effect of local cooling (15 degrees C for 24 hours) with the Chillerpad after traumatic brain injury in the nonhuman primate. Adv Exp Med Biol 578:311-315, 2006.
- 36. Poloyac SM, Zhang Y, Bies RR, Kochanek PM, Graham SH: Protective effect of the 20-HETE inhibitor HET0016 on brain damage after temporary focal ischemia. J Cereb Blood Flow Metab 26:1551-1561, 2006.
- 37. Rittenberger JC, Hostler DP, Tobin T, Gaines J, Callaway CW: Predictors of ROSC in witnessed aeromedical cardiac arrests. Resuscitation (in press).
- 38. Rittenberger JC, Martin JR, Kelly LJ, Roth RN, Hostler D, Callaway CW: Inter-rater reliability for witnessed collapse and presence of bystander CPR. Resuscitation 70:410-415, 2006.
- 39. Rittenberger JC, Menegazzi JJ, Callaway CW: Association of delay to first intervention with return of spontaneous circulation in a swine model of cardiac arrest. Resuscitation. 73:154-60, 2007.
- 40. Sachse KT, Jackson EK, Wisniewski SR, Gillespie DG, Puccio AM, Clark RS, Dixon CE, Kochanek PM: Increases in cerebrospinal fluid caffeine concentration are associated with favorable outcome after severe traumatic brain injury in humans. J Cereb Blood Flow Metab (in press).
- 41. Shore PM, Berger RP, Varma S, Janesko KL, Wisniewski SR, Clark RS, Adelson PD, Thomas NJ, Lai YC, Bayır H, Kochanek PM: Cerebrospinal fluid biomarkers versus Glasgow coma scale and Glasgow outcome scale in pediatric traumatic brain injury: The role of young age and inflicted injury. J Neurotrauma 24:75-86, 2007.
- 42. Shore PM, Hand LL, Roy L, Trivedi P, Kochanek PM, Adelson PD: Reliability and validity of the Pediatric Intensity Level of Therapy (PILOT) scale: A measure of the use of intracranial pressure-directed therapies. Crit Care Med 24:75-86, 2007.
- 43. Stippler M, Fischer MR, Puccio AM, Wisniewski SR, Carson-Walter EB, Dixon CE, Walter KA: Serum and cerebrospinal fluid magnesium in severe traumatic brain injury outcome. J Neurotrauma (in press).
- 44. Tehranian R, Rose ME, Vagni V, Griffith RP, Wu S, Maits S, Zhang X, Clark RS, Dixon CE, Kochanek PM, Bernard O, Graham SH: Transgenic mice that overexpress the anti-apoptotic Bcl-2 protein have improved histological outcome but unchanged behavioral outcome after traumatic brain injury. Brain Res 1101:126-135, 2006.
- 45. Tortorici MA, Kochanek PM, Poloyac SM: Effects of hypothermia on drug disposition, metabolism, and response: A focus of hypothermia-mediated alterations on the cytochrome P450 enzyme system. Crit Care Med (in press).
- Tyurin VA, Tyurina YY, Osipov AN, Belikova NA, Basova LV, Kapralov AA, Bayır H, Kagan VE: Interactions of cardiolipin and lyso-cardiolipins with cytochrome c and tBid: Conflict or assistance in apoptosis. Cell Death Differ 14:872-875, 2007.
- 47. Tyurina YY, Basova LV, Konduru NV, Tyurin VA, Potapovich AI, Cai P, Bayır H, Stoyanovsky D, Pitt BR, Shvedova AA, Fadeel B, Kagan VE: Nitrosative stress inhibits the aminophospholipid translocase resulting in phosphatidylserine externalization and macrophage engulfment: implications for the resolution of inflammation. J Biol Chem 282:8498-8509, 2007.
- 48. Venneti S, Wagner AK, Wang G, Slagel SL, Chen X, Lopresti BJ, Mathis CA, Wiley CA: The high affinity peripheral benzodiazepine receptor ligand DAA1106 binds specifically to microglia in a rat model of traumatic brain injury: Implications for PET imaging. Exp Neurol (in press).
- 49. Wagner AK, Kline AE, Ren D, Willard LA, Wenger MK, Zafonte RD, Dixon CE: Gender associations with chronic methylphenidate treatment and behavioral performance following experimental traumatic brain injury. Behav Brain Res 2007 Apr 20; [Epub ahead of print].
- 50. Wagner AK, McElligott J, Chan L, Wagner EP, Segal N, Gerber NH: How gender impacts career development and leadership in rehabilitation medicine: Report from the AAPM&R Research Committee. Arch Phys Med Rehabil. (in press).

- 51. Wagner AK, Postal BA, Darrah SD, Chen X, Khan AS: Deficits in novelty exploration after controlled cortical impact. J Neurotrauma (in press).
- 52. Wagner AK, Ren D, Conley YP, Ma X, Kerr ME, Zafonte RD, Puccio AM, Marion DW, Dixon CE: Sex and genetic associations with cerebrospinal fluid dopamine and metabolite production after severe traumatic brain injury. J Neurosurg 106:538-547, 2007.
- 53. Yan HQ, Ma X, Chen X, Li Y, Shao L, Dixon CE: Delayed increase of tyrosine hydroxylase expression in rat nigrostriatal system after traumatic brain injury. Brain Res 1134:171-179, 2007.
- 54. Zhang X, Alber S, Watkins SC, Kochanek PM, Marion DW, Graham SH, Clark RS: Proteolysis consistent with activation of caspase-7 after severe traumatic brain injury in humans. J Neurotrauma 23:1583-1590, 2006.
- 55. Zhang X, Chen Y, Ikonomovic MD, Nathaniel PD, Kochanek PM, Marion DW, DeKosky ST, Jenkins LW, Clark RS: Increased phosphorylation of protein kinase B and related substrates after traumatic brain injury in humans and rats. J Cereb Blood Flow Metab 26:915-926, 2006.

CHAPTERS, EDITORIALS & INVITED PAPERS

- 1. Dennis AM, Kochanek PM: Pathobiology of Blast Injury. Yearbook of Intensive Care and Emergency Medicine, J. L. Vincent (ed). Springer-Verlag, Berlin. pp. 1011-1022, 2007.
- 2. Fink EL, Callaway CW, Tisherman SA, Kochanek PM: Winning the cold war: inroads into implementation of mild hypothermia after cardiac arrest in adults from the European Resuscitation Council Hypothermia After Cardiac Arrest Registry Study Group. Crit Care Med 35:1199-1202, 2007.
- 3. Fink EL, Callaway CW, Tisherman SA, Kochanek PM: Hypothermia in traumatic brain injury. Crit Care Med (in press).
- 4. Howell G, Tisherman SA: Management of Sepsis. Surg Clin North Am 86:1523-1539, 2006.
- Jenkins LW, Kochanek PM: Developmental neurobiology and neurophysiology and the PICU. In: <u>Roger's Textbook of</u> <u>Pediatric Intensive Care, 4th Edition</u>, DG Nichols, et al (eds), Lippincott Williams & Wilkins, Philadelphia, Chapter 51, in press.
- 6. Kochanek PM: Pediatric traumatic brain injury: quo vadis? Dev Neurosci 28:244-255, 2006.
- Kochanek PM, Bayır H, Berger RP, Dixon CE, Jenkins L, Kline AE, Tisherman S, Wagner AK, Clark RSB: The Safar Center for Resuscitation Research: Searching for Breakthroughs in the New Millennium. (Invited Review) General Reanimatology 11(5-6):15-25, 2006.
- 8. Kochanek PM, Bayır H, Jenkins LW, Clark RSB: Molecular biology of brain injury In: <u>Roger's Textbook of Pediatric</u> <u>Intensive Care, 4th Edition</u>, DG Nichols, et al (eds), Lippincott Williams & Wilkins, Philadelphia, Chapter 52, in press.
- 9. Kochanek PM, Berger RP, Margulies S, Jenkins LW: Inflicted Childhood Neurotrauma: New sight into the detection, pathobiology, prevention, and treatment of our youngest patients with traumatic brain injury. (Foreword) J Neurotrauma: *Special issue on inflicted childhood neurotrauma* 24:1-4, 2007.
- 10. Kochanek PM, Forbes ML, Ruppel R, Bayır H, Adelson PD, Clark RSB: Severe TBI in infants and children In: 3rd Edition of Pediatric Critical Care, Fuhrman B, Zimmerman J (eds.), Elsevier Science, St. Louis, Chapter 107, pp 1595-1617, 2006.
- 11. Wagner AK: Conducting Research in Traumatic Brain Injury: Current Concepts and Issues. In: <u>Brain Injury Medicine</u>. Zafonte RD and Zasler N (eds.), Demos Publishing chap 5, pp 33-42, 2006.



Mrs. Audrey L. Berkebile Paul Berkebile, MD Robert William Hickey, Jr., MD Mrs. Wendy West Hickey Jan D. Smith, MD Mrs. Ann S. Snyder James V. Snyder, MD United Way of Allegheny County

UNIVERSITY OF PITTSBURGH



SAFAR CENTER FOR RESUSCITATION RESEARCH

Department of Critical Care Medicine University of Pittsburgh - School of Medicine

> 3434 Fifth Avenue University of Pittsburgh Pittsburgh, PA 15260 USA

Phone: 412.383.1900 Fax: 412.624.0943 Email: kochanekpm@ccm.upmc.edu Website: www.safar.pitt.edu