



SAFAR CENTER FOR RESUSCITATION RESEARCH

2004/2005 ANNUAL REPORT

DEPARTMENT OF CRITICAL CARE MEDICINE
UNIVERSITY OF PITTSBURGH
SCHOOL OF MEDICINE



Safar Center for Resuscitation Research

2004/2005 Annual Report

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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 of CNS Injury. Center investigators work closely with the 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.

Featured on the cover: (top panel) Associate Directors of the Safar Center (from left to right) Drs. Hülya Bayır, Patrick Kochanek (Director), Samuel Tisherman, Larry Jenkins, C. Edward Dixon, Amy Wagner, Clifton Callaway, Anthony Kline, and Robert Clark. (bottom panel) Two-dimensional gel electrophoresis of proteins in developing rat brain after controlled cortical impact injury (from the work of Dr. Larry Jenkins and associates at the Safar Center).

A Letter from the Director...



scientists interested in a career in pediatric neurointensive care and resuscitation-related research.

As this year came to a close, we began moving into our newly renovated center. We have acquired ~8000 square feet of new office and laboratory space, increasing our Center to 20,000 square feet. This greatly enhances our research capabilities. Special thanks to Dr. Mitchell Fink, and Susan Stokes, Chairman and Executive Administrator, respectively, of the Dept. of Critical Care Medicine for supporting this project. I would also like to thank Drs. Dade Lunsford and Ross Zafonte, for support from the Depts. of Neurological Surgery, and Physical Medicine and Rehabilitation, respectively. Finally, I would like to acknowledge the support of Dr. Arthur Levine, Sr. Vice Chancellor for the Health Sciences and Dean of the University of Pittsburgh School of Medicine. I also thank Frank Adams, Doug Schlauch, Kelly Brown, and Dick Aradine, the architects and administrators involved in our renovation, and David Ketter, our facility manager. Our multidisciplinary Center houses faculty from many depts.—and we hope to continue to expand our scope in this regard.

The 2004/2005 academic year was an outstanding one for the Safar Center for Resuscitation Research. We have taken a new approach to our annual report streamlining the sections addressing each of the individual programs, to produce a much more reader-friendly product. We hope that you enjoy the report and its “new look.”



Awards and Accomplishments of Trainees and Faculty

This year, fellow Xianren Wu, MD topped the list for the most important academic achievement at our Center by winning the Young Investigator Award from the Society of Critical Care Medicine (SCCM). He received this prestigious award for his paper titled “Suspended animation with delayed resuscitation allows intact survival from cardiac arrest resulting from prolonged lethal hemorrhage in dogs” which was presented at the 34th SCCM Congress in 2005. His paper was published in the journal *Circulation* and represents further development of a novel resuscitation strategy for combat casualty victims of otherwise lethal hemorrhage. The approach is now called Emergency Preservation and Resuscitation (EPR) by our group. His findings were discussed in detail in last year’s report and involve rapid cooling to temporarily (for 1-2 hours) preserve an injured victim—allowing for a delayed resuscitation. Congratulations to Dr. Wu for winning the highest award to a trainee given by the SCCM. He is now in the Anesthesiology residency program at the University of Pittsburgh School of Medicine.

Congratulations to Dr. Ericka Fink for her research in pediatric critical care. She received the top prize at the fellow’s research day hosted by the American Heart Association, Pennsylvania/Delaware Affiliate. Her presentation was titled “Brief induced hypothermia improves outcome in a pediatric model of asphyxial cardiopulmonary arrest in rats. She is currently in her second year of support on our National Institute of Child Health and Human Development funded T-32 program in neurointensive care research, and is mentored by Dr. Robert Clark. Dr. Fink also received the 2004 Nancy Caroline Fellow Award at the Safar Center. That award is given annually to the fellow at the Safar Center who has made the greatest contribution to the field of resuscitation research. Ericka has accepted a faculty position in our Dept. of Critical Care Medicine.



Drs. Mindy Fiedor (left) and Ericka Fink at the 2005 American Heart Association Gala at the Pittsburgh Hilton



A special accomplishment was the anniversary of 50 years of service by S. William (Bill) Stezoski to the University of Pittsburgh. Bill began working as a laboratory assistant at the University of Pittsburgh in 1955 in the Dept. of Biochemistry and Nutrition in the Graduate School of Public Health. After working briefly at the University of St. Louis in 1965, Bill returned to Pitt and worked in the Dept. of Medicine (Cardiology) until 1972. Ultimately he began working for the late Dr. Peter Safar in 1972. Bill has contributed as a co-author to over 50 publications in medical literature and has helped mentor over 30 research fellows. He is a rare individual who achieved a faculty position as a Research Assistant Professor at the University of Pittsburgh School of Medicine—despite not having a doctoral degree. Bill has unsurpassed technical research experience, and is a tremendous asset to our Center and its trainees. He will be retiring from his faculty position at the end of the 2005-2006 academic year.

**S. William (Bill) Stezoski,
Research Assistant Professor,
University of Pittsburgh
School of Medicine,
celebrates the remarkable
milestone of 50 years of
service to the University.**



Christopher Washington, a medical student at the University of Pittsburgh, studied with Dr. Kochanek for a research elective in 04/05. Chris' research focused on the role of caffeine in experimental and clinical traumatic brain injury. He presented his findings at the Annual Meeting of the National Neurotrauma Society—reporting that chronic caffeine administration attenuated neuronal death after brain injury in mice. He was funded by NINDS. Congratulations to Chris for a terrific job.

Three undergraduate students working with Dr. Amy Wagner in our Rehabilitation Program received awards this year. Joshua Sokoloski was a 2004 National Neurotrauma Society Student Competition Finalist and received a 2004 National Neurotrauma Society Travel Award for his work titled "*In vivo Electrochemical Analysis of Methylphenidate on Striatal Dopamine Neurotransmission after Experimental TBI: An Initial Analysis.*" Zack Repanshek received a Chancellor's Award for Undergraduate Research and Undergraduate Travel Scholarship for his research on "*The Effects of Caffeine on Striatal Dopamine Neurotransmission after Experimental TBI.*" Megan Andes received a 2004 University of Pittsburgh Research Experience for Undergraduates Scholar Award and a 2005 American Chemical Society Travel Award for her work titled "*Effects of Single Dose Methylphenidate Treatment on Striatal Dopamine and Metabolite Levels after Experimental TBI.*" Hearty congratulations to each of these students and to Dr. Wagner who is an exceptionally talented mentor.

Our trainees produced many accomplishments. Dr. Paul Shore published a report in the *Journal of Neurotrauma* comparing the use of intermittent versus continuous cerebrospinal fluid drainage after traumatic brain injury in children. He was also funded by our training grant from the National Institute of Child Health and Human Development. Paul is now on the faculty of the University of Texas Southwestern Medical Center and is pursuing a career focused on clinical research in pediatric neurointensive care. Dr. Margaret Satchell, who completed her research training in July 2002, published a paper in the *Journal of Cerebral Blood Flow and Metabolism* titled "Cytochrome C, a biomarker of apoptosis, is increased in cerebrospinal fluid from infants with inflicted brain injury from child abuse." That report resulted from her work under the mentorship of Dr. Robert Clark and describes an important association between child abuse and increases in the apoptosis-triggering mitochondrial protein cytochrome-C. Her work may identify a novel therapeutic target in inflicted traumatic brain injury.



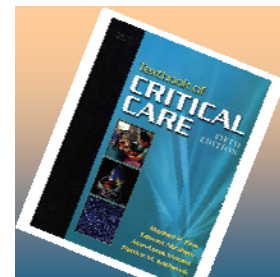
Dr. Xiaopeng Zhang with technicians Keri Feldman (left) and Christina Marco (right).

Dr. Hülya Bayır, Assistant Professor of Critical Care Medicine, working on an NIH-funded project, reported endogenous antioxidant effects of inducible nitric oxide synthase – derived from nitric oxide in an experimental model of traumatic brain injury. Her studies were done in collaboration with Dr. Valerian Kagan of the University of Pittsburgh Center for Free Radical and Antioxidant Health. Notably, one of the figures from Dr. Bayır's work was selected for the cover of the June 2005 issue of the *Journal of Cerebral Blood Flow and Metabolism*.

We will miss Dr. Xiaopeng Zhang, a talented scientist who worked in the laboratory of Dr. Robert Clark at our Center. Xiaopeng's accomplishments in the area of mechanisms of neuronal death were exceptional. He authored a number of manuscripts and has several reports in submission and preparation.

Dr. Zhang accepted a position in the Anesthesiology residency program at the Massachusetts General Hospital. We cannot thank him enough for the superb job that he did at the Safar Center.

Another accomplishment was publication of the 5th edition of the "Textbook of Critical Care Medicine." Dr. Kochanek was one of the four editors of this premier textbook along with Drs. Mitchell Fink, Ed Abraham and Jean-Louis Vincent. This book evolved from the initial Shoemaker textbook of critical care, edited by Dr. Ake Grenvik, Distinguished Service Professor and former chief of our CCM Division. It is an honor to carry on the tradition of this textbook in Pittsburgh. Twelve Safar Center investigators and trainees contributed as authors of the new edition of the textbook. Special thanks to Dr. Mitchell Fink who spearheaded this project. I also thank Marci Provins for her administrative assistance with my contributions to the textbook.



New Grants

This year, we began an important new initiative at the Safar Center. In March of 2005, Dr. Kochanek submitted as PI, a program project grant to the United States Army Peer Reviewed Medical Research Program titled “Novel Nitroxide Resuscitation Strategies in Experimental Traumatic Brain Injury.” This project involves a collaboration between the Safar Center for Resuscitation Research, Synzyme Technologies in Irvine, California, The University of Pittsburgh Center for Free Radical and Antioxidant Health, the University of Pittsburgh Brain Trauma Research Center, and the Pittsburgh NMR Center for Biomedical Research. The focus of the proposal is to test several novel resuscitation fluids including polynitroxylated albumin and polynitroxylated hemoglobin in an experimental model of traumatic brain injury combined with hemorrhagic shock. We are targeting the recent epidemic of blast-induced traumatic injury seen in both United States combat casualties in the Iraq war and civilian victims of terrorist attacks resulting from improvised explosive devices (IEDs). Drs. Carlton Hsia and Li Ma are co-investigators at Synzyme Technologies. I am pleased to say that during the preparation of this report, this \$2 million grant was funded and work has just begun. We look forward to tackling this critical emerging challenge in military and civilian trauma.

Among the other grants obtained this year, Dr. Tomas Drabek was funded by the Laerdal Foundation for his work on the development of a model of EPR in rats. This project builds on the rich tradition of investigation of ultra-novel approaches to the treatment of exsanguination cardiac arrest initiated by the late Dr. Peter Safar many years ago. We again are grateful to the Laerdal Foundation for its unwavering support of our young investigators.

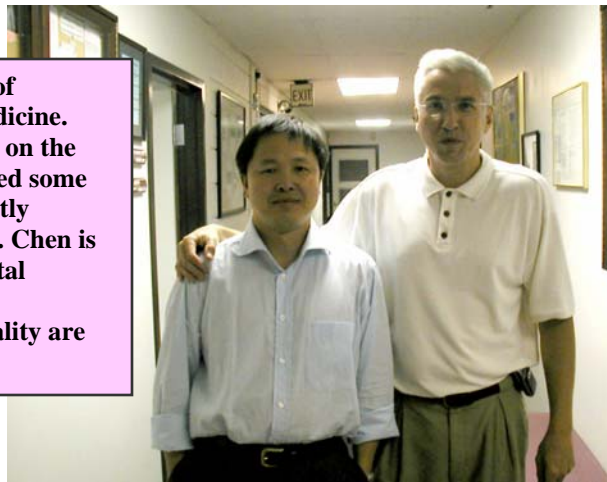
New Associate Director and Scientists at the Safar Center

This year, Dr. Hülya Bayır joined our group of associate directors for the Center. Dr. Bayır is an emerging star in the application of free radical biology to CNS injury. She trained under Dr. Valerian Kagan, Director of the University of Pittsburgh Center for Free Radical and Antioxidant Health, and has masterfully strengthened the link between Dr. Kagan’s Center and the Safar Center through a number of valuable collaborations on both manuscripts and grants. Dr. Bayır is also a talented intensive care specialist at Children’s Hospital, and provides additional bench to bedside expertise to our Center.

We also welcomed Dr. Weimin Gao to our Center as a new scientist. Weimin has considerable expertise in proteomics and comes from the prestigious proteomics group at the University of Michigan, where he trained under Dr. Gilbert Omenn, among others. He will work in the area of proteomics applications to child abuse.

Guest Professors

We hosted Jiang-Fan Chen, MD, PhD, Dept. of Neurology at Boston University School of Medicine. Dr. Chen has been carrying out seminal work on the adenosine A2a receptor in stroke and presented some of his recent findings. His research was recently published in the journal *Nature Medicine*. Dr. Chen is collaborating with us on studies in experimental traumatic brain injury. His presentation was outstanding and his collaboration and collegiality are greatly appreciated.



In March 2005, Damir Janigro, PhD, from the Dept. of Neurosurgery at the Cleveland Clinic Foundation also visited our Center and presented his work on the blood-brain barrier and biomarkers of brain injury. His presentation titled “Measuring the Human Blood-Brain Barrier: MRI vs Serum Markers” was valuable to a number of investigators in our Center interested in the area of biomarkers in brain injury, proteomics, and child abuse.

Drs. Jiang-Fan Chen and Patrick Kochanek

Special Events

Finally, on June 23 and 24, 2005 the Safar Center hosted the 4th Safar Symposium, the 25th Peter and Eva Safar Annual Lectureship in Medical Sciences and Humanities, and a special Consortium for the Clinical Application of EPR. Details of these special events are addressed later in this report.

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, Val Sabo, and Julian Smith for their administrative and secretarial excellence. Marci also serves as my local editorial assistant for the journal *Pediatric Critical Care Medicine*. Fran Mistrick coordinates the annual Safar Symposium and is developing a historical display in the new Safar Conference room in our Center. More on that in next year's report. I also thank Henry Alexander, John Melick, Keri Feldman, Vincent Vagni, Xiecheng Ma, Dr. Lina Du, Paula Nathaniel, Ray Griffith, Grant Peters, 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, Callaway, Clark, Dixon, Jenkins, Kline, Tisherman, and Wagner for their assistance. These Associate Directors have made special contributions to our success. I also thank Drs. Rachel Berger and David Adelson for their work in child abuse and pediatric traumatic brain injury, respectively. Thanks are also due to Drs. John Williams, Dade Lunsford, Ross Zafonte, Paul Paris, David Perlmutter, Xiaopeng Zhang, Hong Yan, Miro Klain, Steven Graham, Steven DeKosky, and Robert Hickey for their assistance. I am especially thankful to Dr. Ann Thompson for her continued support and guidance.

I am also 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 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 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 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 Vandred, Director of combat casualty care research at the United States Army Medical Research and Materiel Command, and Mr. Robert Read at TATRC for their efforts on behalf of our Center and its investigators. I thank Dr. Lyn Yaffe of Alion Sciences. Lyn is a long-time supporter and collaborator who has contributed in many ways to our success.

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

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 toward Dr. Safar's goal of the resuscitation of "brains and hearts too good to die."

I once again look forward to success in 2005/2006 in our investigative efforts to develop new therapies in the field of resuscitation medicine, and thank you for your continued support of our work.

Respectfully submitted,

Patrick M. Kochanek, MD



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

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

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
 Rachel Berger, MD
 Nicholas Bircher, MD
 Miroslav Klain, MD, PhD
 S. William Stezoski
 Xiaopeng Zhang, MD

Guest Scientists

Steven DeKosky, MD
 Lina Du, MD
 Howard Ferimer, MD
 Robert Garman, DVM
 Steven Graham, MD, PhD
 Kristy Hendrich, BS
 Robert Hickey, MD
 Sam Poloyac, PhD
 James V. Snyder, MD
 Stephen R. Wisniewski, PhD
 Hong Qu Yan, MD

Visiting Scientists

Ernesto A. Pretto, MD
 Ann Radovsky, DVM, PhD
 Lyn Yaffe, MD

Fellows

Amanda Al-Khalidi, PhD
 Mandeep Chadha, MD*
 Xiangbai Chen, MD, PhD
 Tomas Drabek, MD
 Melinda Fiedor, MD*
 Ericka Fink, MD*
 Yi-Chen Lai, MD*
 Margaret Wilson, PhD
 Xianren Wu, MD

Support Staff

Linda Amick
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 Valerie Sabo
 Julian Smith

Technicians

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 Henry Alexander
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 Sherman Culver
 Dwight Davis
 Holly Donovan
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 Yaoqiong Hao
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 Keri Janesko
 Danielle Kausler
 Youming Li
 Xiecheng Ma, MD
 Christina Marco
 John Melick
 Paula Nathaniel
 Dan Santone
 Jason Stezoski
 Vince Vagni

Students

Adib Abl
 Amber Casey
 J'Mir Cousar
 Laura Drewenicki
 Nikhil J. George
 Ashley Grosvenor
 Lauren Kmec
 Scott Kunkel
 George Nikhil
 Zachary Repanshek
 Kathleen Sachse
 Ryan Santos
 Josh Sokoloski
 Chris Stangey
 Michael Tortorici
 Matthew Tormenti
 Mike Wenger
 Lauren Willard

* denotes current T32 fellow

FINANCIAL HIGHLIGHTS

During the 2004/2005 academic year, Safar Center investigators had a total of 28 active grants. Twenty five of these grants were extramural. The direct and indirect costs for the full award period of these grants totaled **\$27,936,069** and this is plotted below for the current and preceding ten academic years.

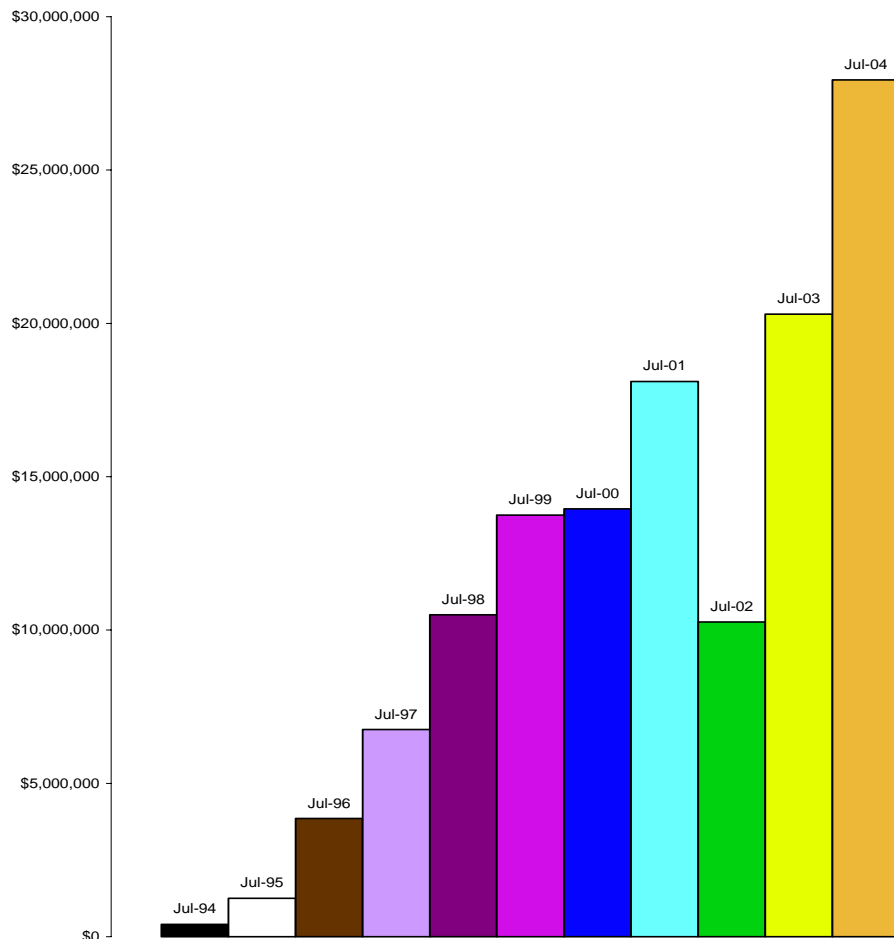
The specific sources of this grant support are shown on the subsequent page. Remarkably, the Safar Center is continuing to grow and maintain a high level of extramural support. This continues to require a monumental effort by our faculty since our support is almost completely derived from extramural grants. Congratulations to the faculty for their funding successes.

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.

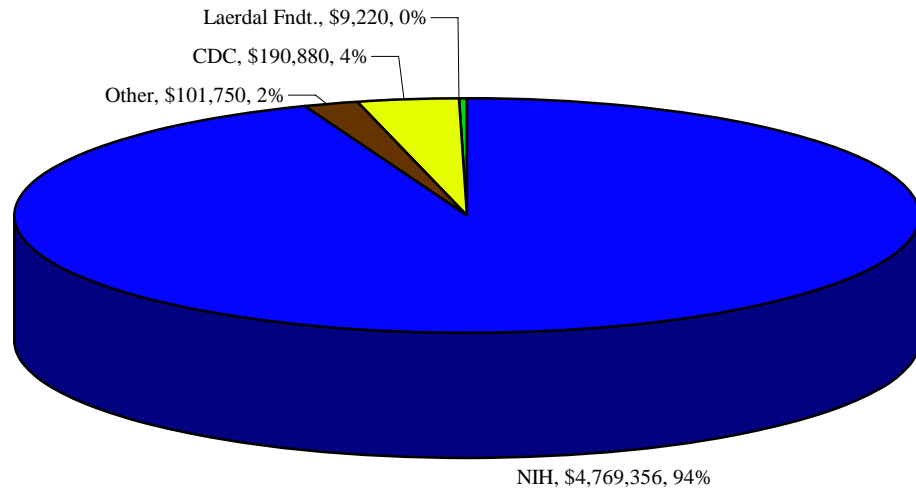
Extramural funding sources included the National Institutes of Health, the Centers for Disease Control and Prevention, the Laerdal Foundation, and a variety of other sources. Intramural funding was provided by the Departments of Critical Care Medicine, and Anesthesiology, and the Children's Hospital of Pittsburgh.

We are deeply grateful for the prior and current support from all of these granting agencies.

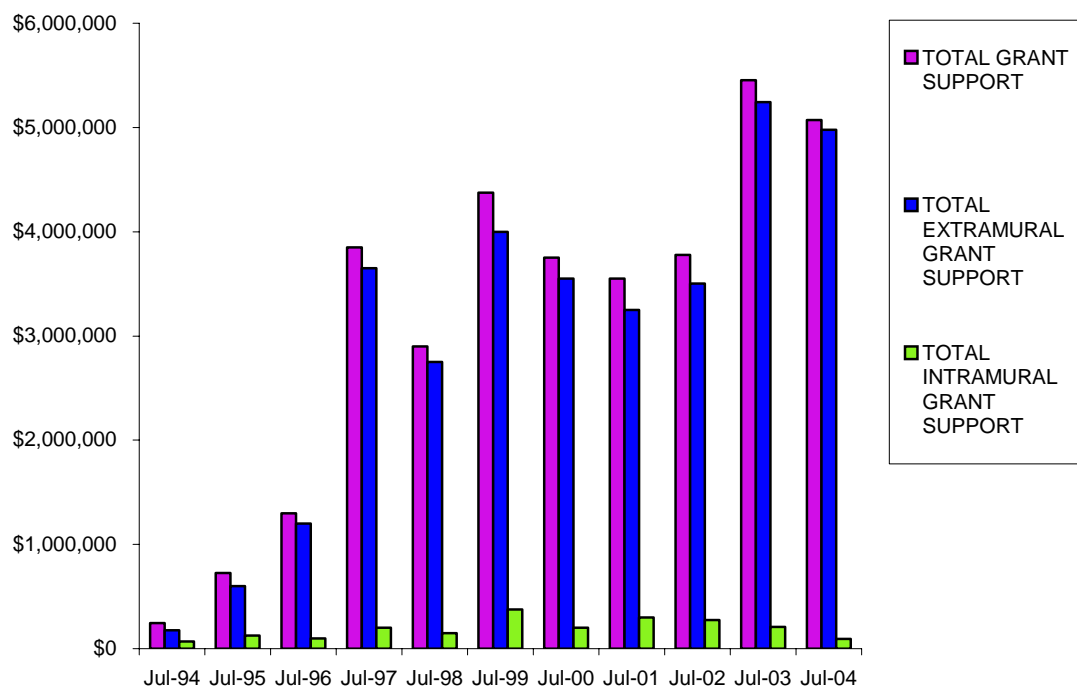
**Direct and Indirect Costs for the
Full Award Period of SCRR Grants**



Specific Sources of Grant Support for 2004/2005



Safar Center Grant Support 1994/1995 through 2004/2005 (Funds available for each fiscal year)



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 of only 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 was recently launched and involves testing of novel polynitroxylated albumin and hemoglobin solutions, among other therapies. This project will be discussed further in the section on “Combat Casualty Care.”

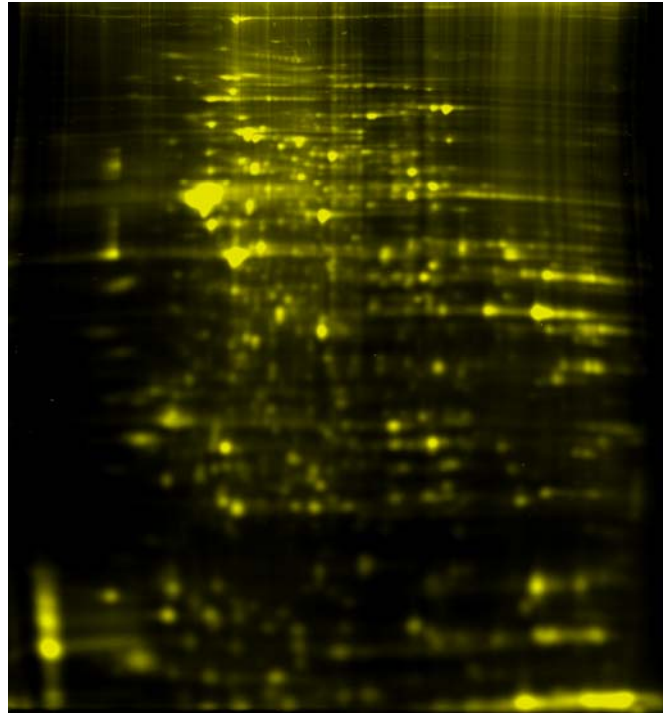
Many other federally-funded projects on TBI are being carried out at the Safar Center. NIH-funded research is directed toward the development of new treatments, such as agents targeting the adenosine, apoptosis, dopamine, kinases, protein synthesis, or serotonin pathways, among others. Some of the most promising studies at the Safar Center with regard to new therapies for TBI include the work of Dr. Robert Clark with PARP antagonists and Dr. Anthony Kline with serotonin 1A receptor agonists.

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.

Safar Center Scientists are studying how the brain responds to traumatic injury and are developing and testing new treatments to improve outcome. Experimental models of TBI are being used and a bench to bedside approach has been a trademark at our center. Key mechanisms of secondary damage in the brain after human head injury are also being identified by applying molecular and biochemical methods to human



Safar Center scientist Dr. Larry Jenkins and his team are using proteomics approaches—such as 2-D gel shown above—to unravel the complex biology of the injured brain and identify new therapeutic targets in patients after TBI.

In 2004-2005, Safar Center investigators authored 17 peer-reviewed manuscripts on TBI. Among the highlights was Dr. Hülya Bayır's work on inducible nitric oxide synthase –which garnered the cover of the *Journal of Cerebral Blood Flow and Metabolism*, and a bench-to-bedside review on apoptosis in TBI by Dr. Xiaopeng Zhang published in *Critical Care*. Our group also authored the chapter on severe TBI in infants in the 3rd edition of the Fuhrman-Zimmerman Textbook of Pediatric Critical Care—one of the premier textbooks in the field of pediatric critical care medicine.

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



Dr. Rachel Berger

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. 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.

Our preliminary investigations suggest that this approach is feasible. Additional clinical trials of these new diagnostic tests are underway. Among the publications by our group this year, Drs. Berger and Kochanek at the Safar Center and Dr. Mary-Clyde Pierce at the University of Louisville published an invited review on this novel approach in the journal *Child Abuse and Neglect*.

“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.”

The development of a blood test that could be used as a screening tool for this condition is an area of research by Safar Center investigators.

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.

Dr. Margaret Satchel, working in the laboratory of Dr. Clark, reported in the *Journal of Cerebral Blood Flow and Metabolism* that infants who are victims of inflicted childhood neurotrauma had unusually high levels of the protein cytochrome-C in their cerebrospinal fluid after injury. Since cytochrome-C is an important trigger of the death of neurons by apoptosis, this suggests that the apoptotic neuronal death pathway might be of special importance as a new therapeutic target in inflicted childhood neurotrauma. This line of investigation represents an important potential area for future research.

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

**We are one of
only a few
centers in the
world that are
carrying out
systematic
studies of novel
diagnostic and
therapeutic
approaches to
inflicted
childhood
neurotrauma**

CARDIAC ARREST

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.

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 has led an impressive bench-to-bedside effort in this area ranging in scope from the study of the mechanisms underlying neuronal damage after cardiac arrest in experimental animal models to clinical trials of new therapies, such as vasopressin and hypothermia. Highlights this year from his group include a report in the journal *Brain Research* on the effects of hypothermia on brain-derived neurotrophic factor production in experimental cardiac arrest, a manuscript in the journal *Resuscitation* describing the success of combined vasopressin and epinephrine in clinical cardiac arrest, and reviews by Drs. Callaway and Hostler on future directions in resuscitation in the *Journal of Emergency Medical Services*, and Drs. Callaway and Menegazzi on waveform analysis of ventricular fibrillation in *Current Opinion in Critical Care*. Finally, Dr. Callaway authored the chapter on resuscitation in the new edition of the *Shoemaker Textbook of Critical Care Medicine* (please see the introductory letter of this report).

Cardiopulmonary arrest in infants and children

Dr. Robert Clark leads a team of investigators at the Safar Center and Children's Hospital of Pittsburgh who are focused on the development of new therapies to mitigate neurological damage after asphyxial arrest in children. Unlike adults, 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, T-32 fellow Dr. Ericka Fink reported in the journal *Developmental Neuroscience* that mild hypothermia attenuates neurological injury in this model. Mild hypothermia, recently approved by the American Heart Association for use in adults with ventricular fibrillation is likely to go to clinical trials in children.



Dr. Robert Clark's group has developed a clinically realistic animal model of asphyxial cardiac arrest, mimicking cardiac arrest in children. Research in this model is funded by NIH, and is being used to evaluate new therapies that may be candidates for clinical trials.

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.

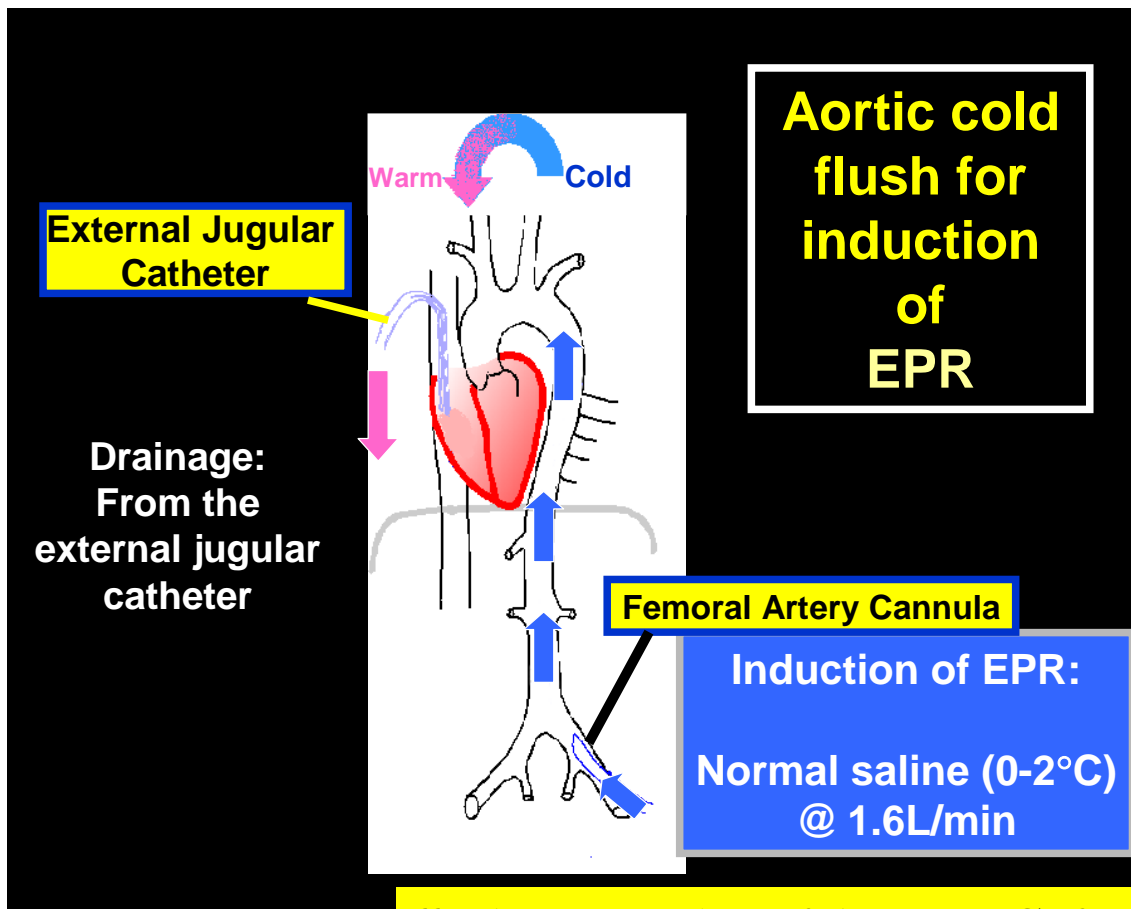
Faculty Principal Investigators

Clifton Callaway, MD, PhD
Hülya Bayır, MD
Samuel A. Tisherman, MD

Robert S.B. Clark, MD
Robert Hickey, MD
Patrick M. Kochanek, MD



Historic photo of the birth of CPR in 1956 depicting the late Dr. Peter Safar crouched at left explaining his newly crafted approach to mouth-to-mouth resuscitation. Dr. Safar's pioneering work has saved millions of lives.



“I bet people said Peter Safar was silly when he invented closed-chest CPR. Anybody that’s silly enough to bet against Peter Safar is a very foolish individual. If he says it will work, it will work. Now it’s just a matter of making it happen.”

Dr. Thomas Scalea, Physician-in-Chief of the internationally acclaimed, R Adams Cowley Shock Trauma Center, University of Maryland Medical Center

Pittsburgh Tribune Review - 6/29/05

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.

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. Ala Nozari published an important report on EPR in the *Journal of Trauma*, demonstrating that good outcome could be achieved with a 60 min period of hypothermic preservation even if tissue trauma were included in the model. Dr. Xianren Wu also carried out studies reporting that up to three hours of EPR could be achieved if energy substrates were added to the flush. Addition of the combination of dissolved oxygen and glucose to the flush has afforded the best outcomes thus far in our center. Dr. Wu’s important study was presented at the 2005 meeting of the International Anesthesia Research Society (IARS).

In addition, Dr. Tomas Drabek carried out the first studies of EPR in a rat model of exsanguination cardiac arrest. With the aid of Drs. Hillary Grocott and David Warner at Duke University, who helped us establish cardiopulmonary bypass for rats in our Center, Dr. Drabek was able to use EPR to achieve neurologically intact outcome in rats after a 30 minute exsanguination cardiac arrest. That work was presented at the 34th meeting of the Society of Critical Care Medicine. We look to this new model to allow us to study molecular mechanisms during prolonged hypothermic arrests and to screen therapies.



A Clinical Consortium to Discuss a Feasibility Trial of EPR in Civilian Trauma

On June 24, 2005, Dr. Tisherman hosted the first meeting of a consortium of clinical investigators interested in the application of EPR to the victims of otherwise lethal exsanguination cardiac arrest. A group of esteemed trauma surgeons, intensive care specialists, and scientists, along with representatives from the United States Military, and the University of Pittsburgh Institutional Review Board (IRB), among others attended this unique meeting. Attendees included Drs. Hasan Alam, Harvard Medical School; Howard Champion, Tech Med, Inc., Annapolis, MD; Debra Malone (US Air Force), University of Maryland, Frederick Moore, Hermann Hospital/University of Texas, Houston, TX; Aurelio Rodriguez, Allegheny General Hospital, Pittsburgh, PA; Thomas Scalea, R Adams Cowley Shock Trauma Center, Baltimore, MD; Roger Shere-Wolfe, University of Maryland Shock Trauma Center, Martin Schreiber, Oregon Health and Science University, Portland, OR; Wilhelm Behringer, Vienna General Hospital, Vienna, Austria; Lyn Yaffe, Alion Science and Technology; Rockville, MD. Also attending from the US Army Medical Research & Materiel Command were COL Robert Vandre, COL Ron Poropatich and Mr. Robert Read; from the University of Pittsburgh Medical Center were Drs. Clifton Callaway, Edwin Jackson, Miroslav Klain; from the University of Pittsburgh IRB office were Drs. Richard Guido, Christy Rothwell and Ms. Jean Barone; and from the Safar Center Drs. Patrick Kochanek, Xianren Wu, Tomas Drabek and Mr. William Stezoski

A day of productive discussions confirmed that some victims of trauma suffer exsanguination cardiac arrest and might be able to be saved if EPR could be optimized for clinical use. Laboratory research on EPR using the rapid induction of hypothermia followed by damage control surgery and delayed resuscitation was presented. EPR was felt to be ready, after appropriate planning, for clinical trials. Dr. Tisherman led the discussion on the potential entry criteria and the clinical protocol, including defining sample size, equipment needs, and site training. A synopsis of this historic consortium is being prepared as planning for the trial proceeds.

Finally, Drs. Kochanek, Tisherman, Wu, Yaffe and Mr. Stezoski also filed a provisional 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



Dr. Samuel Tisherman

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 initially designed by Dr. Tisherman and the late Dr. Safar, along with a number of research fellows working 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.

“The goal of these studies is to prolong the golden hour of shock and allow survival with good outcome”

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 numerous studies, is mild hypothermia. Mild hypothermia mitigates deleterious cardiovascular effects and cell death cascades during and after shock, and prolongs the golden hour. However, these studies have raised controversy in the shock community, since it has long been known that the occurrence of hypothermia is associated with poor outcome in patients with hemorrhagic shock. Some of the important differences between induced hypothermia and “spontaneous” hypothermia, however, may help explain these controversies. It is likely that although cooling is protective against tissue ischemia during and after shock, it also has adverse consequences on coagulation, and that these consequences may be magnified by the current use of crystalloid resuscitation fluids and packed red blood cells, both of which dilute the natural clotting mechanisms in blood. The need for factor replacement and/or other related pro-coagulant approaches may be a key to allowing the use of mild cooling to protect against ischemic damage. Optimization of mild hypothermia is an important area of future research

Other unique therapeutic approaches to hemorrhagic shock that we have studied include intraperitoneal delivery of oxygen, cooling, and drugs (such as adenosine). Some of these novel approaches have produced exciting findings and are under continued investigation.

This year, using a model of severe lethal hemorrhagic shock in pigs, Dr. Xianren Wu reported that mild hypothermia—induced with room temperature saline—could prolong the golden hour of shock and improve survival. His findings were published in the *Journal of Trauma*.

Faculty

Samuel A. Tisherman, MD
S. William Stezoski

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 current 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, and combinations of these insults is also 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

We have just been awarded a new collaborative program project funded by the United States Army Peer Reviewed Medical Research Program (PRMRP) titled “Novel Nitroxide Resuscitation Strategies in Experimental Traumatic 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 will target 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 will examine conventional and novel resuscitation strategies targeting this important problem.

Our goal is
to develop a
resuscitation
fluid that
limits shock
but is also
“friendly” to
the injured
brain.

Novel polynitroxylated albumin and hemoglobin solutions, among other conventional and novel therapies will be tested. This work includes important additional collaborations with both the Pittsburgh NMR Center for Biomedical Research at Carnegie Mellon University, directed by Dr. Chien Ho and the University of Pittsburgh Center for Free Radical and Antioxidant Health, directed by Dr. Valerian Kagan.

Several additional efforts focused on combat casualty care are in development and we look forward to discussing these in future annual reports.

Faculty

Patrick M. Kochanek, MD

Samuel A. Tisherman, MD

Hülya Bayır, MD

Robert S.B. Clark, MD

C. Edward Dixon, PhD

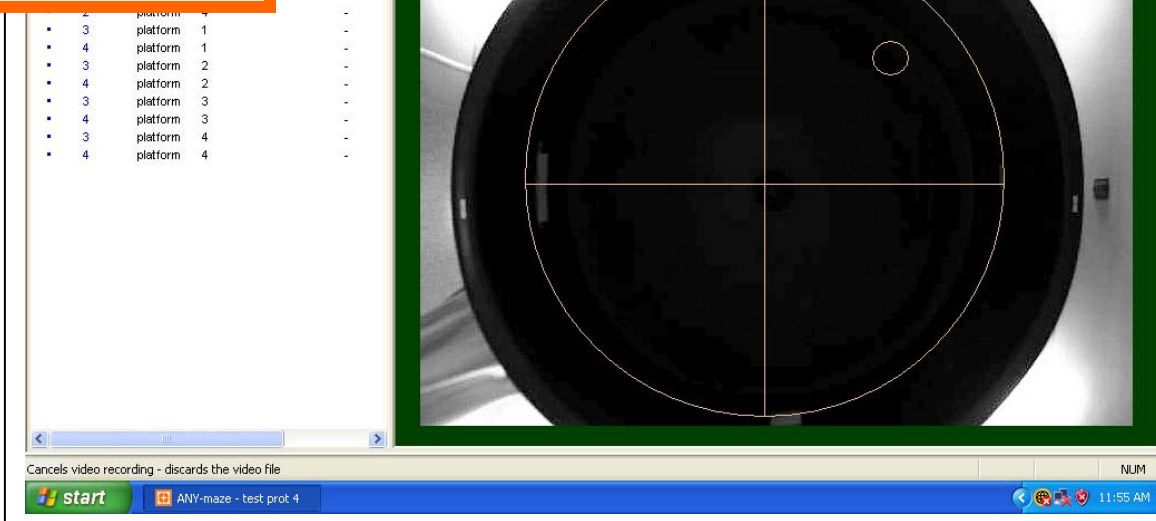
Larry W. Jenkins, PhD



Artistic image of “The Doc” which was used as part of an award presented by the United States Army Medical Research and Materiel Command to Mrs. Eva Safar in recognition of Dr. Peter Safar’s important contributions to combat casualty care. This image is from the “Angles Among Us” series that was designed by Blessings Expressions of Faith (www.blessings-catalog.com).



C. Edward Dixon, PhD



The Safar Center features a state-of-the-art facility for the assessment of motor and cognitive function in rodents that includes five Morris Water Mazes. A schematic of a Morris Water Maze is shown in the figure above. The functional outcome facility at the Safar Center is directed by C. Edward Dixon, a recognized expert in this area of research.

REHABILITATION OF CENTRAL NERVOUS SYSTEM INJURY

Establishment of a formal research program in rehabilitation of central nervous system injury represents an important new direction for 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. Logically, collaboration with investigators in the Dept. of Physical Medicine and Rehabilitation (PM&R) of the University of Pittsburgh School of Medicine has evolved, spearheaded by Drs. C. Edward Dixon and Ross Zafonte, and an outstanding relationship between the Safar Center and Dept. of PM&R has emerged. This culminated in the construction of new laboratory space for the Dept. of PM&R that is dedicated to rehabilitation research at the Safar Center.

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

This year, Dr. Amy Wagner, a Physiatrist in the Dept. of PM&R at the University of Pittsburgh School of Medicine, and Dr. Anthony Kline, a scientist in that same department have been studying the use of enriched environment during the delayed phases after experimental TBI in the controlled cortical impact model in rats. Studies showing significant differences in the response to enriched environment after experimental TBI in male versus female rats represent important findings that could ultimately have implications on the critical need to consider gender differences in the development of clinical trials in brain injury rehabilitation.

Studies are also underway that are examining long-term disturbances in neurotransmitter systems such as the dopaminergic system, the cholinergic system, and the influence of adenosine. 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 newly renovated functional outcome testing center for evaluation of behavioral outcome in animals is a state-of-the-art facility under the direction of Dr. C. Edward Dixon in the Safar Center and includes five Morris water mazes, and other important tools for assessment of long-term motor and cognitive outcome and has been instrumental to these studies linking resuscitation and rehabilitation.

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 research. Research training was a hallmark of Dr. Safar's illustrious career and this tradition continues as a key centerpiece in the Safar Center. A remarkable number 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 across the globe. Established investigators such 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 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.



Drs. Patrick Kochanek and Akira Takasu during Dr. Kochanek's visit to Tokyo, Japan where he served as a keynote speaker for the Japanese Association of Acute Medicine.

Postdoctoral fellow positions are funded by several means including 1) individual grants to principal investigators in the Center, 2) individual fellowship grants to trainees, or 3) a unique T-32 grant from the National Institute of Child Health and Human Development titled "Pediatric Neurointensive Care and Resuscitation Research." The latter 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.

In the last 5 years, nine trainees at the Safar Center have gone on to achieve RO-1s, K-awards, or other substantial national funding (shown below), 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
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 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 accomplishments are outlined in the opening letter from the Center's director. Most notable was selection of fellow Dr. Xianren Wu as recipient of the "Young Investigator Award" by the Society of Critical Care Medicine. Accomplishments of our T-32 fellows including Drs. Mandeep Chadha, Melinda Fiedor, Ericka Fink and Yi-Chen Lai, are also outlined in the opening letter of this report.

Three undergraduate students working with Dr. Amy Wagner in our Rehabilitation Program received awards this year—Joshua Sokoloski, Zack Repanshek and Megan Andes. Details of their awards were presented in my opening letter in this report. Congratulations to each of these students and to Dr. Wagner who has served as a fantastic mentor to these young scientists.

In addition, recent trainees Drs. Margaret Satchell and Dr. Paul Shore published manuscripts in the *Journal of Cerebral Blood Flow and Metabolism* and the *Journal of Neurotrauma*, respectively. Finally, University of Pittsburgh medical student Dr. Christopher Washington worked in the laboratory of Dr. Patrick Kochanek studying the role of adenosine in traumatic brain injury. Funded by a supplement from the National Institute of Neurological Disorders and Stroke, Christopher presented papers at Annual Meetings of the Society for Pediatric Research and the National Neurotrauma Society.

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

The 25th Peter and Eva Safar Annual Lectureship in Medical Sciences and Humanities.

On June 23, 2005, Dr. James Grotta, Roy M. and Phyllis Gough Huffington Professor and Chairman of the Department of Neurology at the Baylor College of Medicine served as the 25th Peter and Eva Safar Lecturer in Medical Sciences and Humanities at the University of Pittsburgh School of Medicine. The innovative work of his



Dr. Grotta has done important work in the area of new therapies for stroke and other forms of brain ischemia and is one of the leading proponents of the concept of increasing public awareness of stroke as a “brain attack.”

group on the use of ultrasound as a potential clot-busting strategy in the emergency treatment of stroke—recently published in the *New England Journal of Medicine* was highlighted in his memorable presentation.

A dinner in honor of Dr. Grotta was held at the Monterey Bay Fish Grotto on Mt. Washington overlooking the city of Pittsburgh. This location has been a tradition for the dinner related to the fact that the late Dr. Safar used this view of the city to recruit over 100 faculty members.



*Standing: Mr. Tore Laerdal, Dr. and Mrs. John Williams
Seated from left: Dr. James Grotta, Dr. and Mrs. Patrick Kochanek, Drs. Susan Dunmire and Samuel Tisherman*

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

The Third 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 specific areas, namely “Breakthroughs in Resuscitation” and “Advances in Human Simulation Education.”

The session on “Breakthroughs in Resuscitation” focused on post-resuscitation inflammation and featured presentations by Dr. W. Dalton Dietrich, Scientific



Edward Hall, PhD

Director of the Miami Project to Cure Paralysis, University of

Miami on “Inflammatory Response to CNS Injury: Effects of Hypothermia,” Dr. Edward Hall, Director of the Spinal Cord and Brain Injury Research Center at the University of Kentucky on “Nitrosative Stress and Damage in CNS Injury,” Dr. Valerian Kagan, Vice Chairman of the Dept. of Environmental and Occupation Health at the University of Pittsburgh, on “Oxidative Lipidomics of Apoptosis and Phagocytosis,” Dr. Hasan Alam, Director of the Trauma, Emergency and Surgical Critical Care

Laboratory at the Massachusetts General Hospital on “Effect of Resuscitation Strategies on Post-Shock Inflammatory Response,” and Dr. Yi-Chen Lai, Research Fellow at the Safar Center on “PARP Activation – A Key Component of the Response to Brain Injury.”

Speakers at the afternoon session on “Advances in Human Simulation Education” included Dr. Joseph Quinlan, Chief Anesthesiologist, University of Pittsburgh Medical Center (UPMC) on “Validation of Anesthesia Difficult Airway Management Competency Assessment,” Dr. Elizabeth Hunt, Director, Johns Hopkins Simulation Center on “Pediatric Mock Codes Using Simulation,” Dr. Michael DeVita, Associate Professor, Dept. of Critical Care Medicine, UPMC on “In-Hospital Crisis Team Training with Simulation,” and Dr. Paul Phrampus, Assistant Director, Emergency Medical Programs in the Winter Institute for Simulation, Education and Research (WISER) at UPMC on “Simulation-Based Emergency Medicine Difficult Airway Management Training.” The afternoon session was organized by Dr. John Schaefer, Director of WISER.

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 and to Lippincott Williams & Wilkins Inc., for their support. Funding was also provided by the Safar Legacy Fund, as well as the Depts. of Anesthesiology, and Critical Care Medicine.

On June 23, 2005, the Safar Center hosted the 3rd Safar Symposium at the University of Pittsburgh School of Medicine. The symposium also features presentation of the annual Nancy Caroline Award—which is presented to the top trainee at the Safar Center, as selected by the Associate Directors of the Center, and is linked to the Peter and Eva Safar Lectureship.



W. Dalton Dietrich, PhD

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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
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