A Trauma Surgeon's Journey Through the World of Basic Research

Hasan B Alam, MD

Norman Thompson Professor of Surgery

Chief of General Surgery. University of Michigan Health Care System

Disclaimers

- Personal stories
- Biased opinions

Academic Surgery

Washington, DC in the 90's

MARION BARRY

"Outside of the killings, Washington has one of the lowest crime rates in the country."

EXTRA!

The Washington Times

FRIDAY, JANUARY 19, 1990 WASHINGTON, D.C. 25 cents

BUSTED

FBI's bait was an ex-lover

Scandal called tragedy for city

Barry vows to fight charges, run city

THE BARRY ARREST

SPECIAL REPORT:

Getting hooked on trauma

Murder Capital

Comparison of the District with 11 other cities
Homicide rates per 100,000 people

	1985	1990	1995	2000	2005
Baltimore	27.6	41.4	45.2	40.1	42.0
Detroit	58.2	56.6	47.6	41.6	39.5
Washington	**23.5**	**77.8**	**65.2**	**41.8**	**35.4**
Philadelphia	16.6	31.7	28.2	21.0	25.6
Dallas	30.2	44.4	26.5	19.4	16.4
Houston	26.2	34.8	18.2	11.8	16.3
Chicago	22.2	30.5	30.0	21.8	15.6
Phoenix	10.0	13.0	19.7	11.5	15.0
Boston	15.2	24.9	17.4	6.6	12.9
San Francisco	11.6	14.0	13.4	7.6	12.8
Los Angeles	24.4	28.2	24.5	14.9	12.6
New York City	19.3	30.7	16.1	8.4	6.6

Washington Hospital Center
Trauma Surgeons Ruled

Early mentor

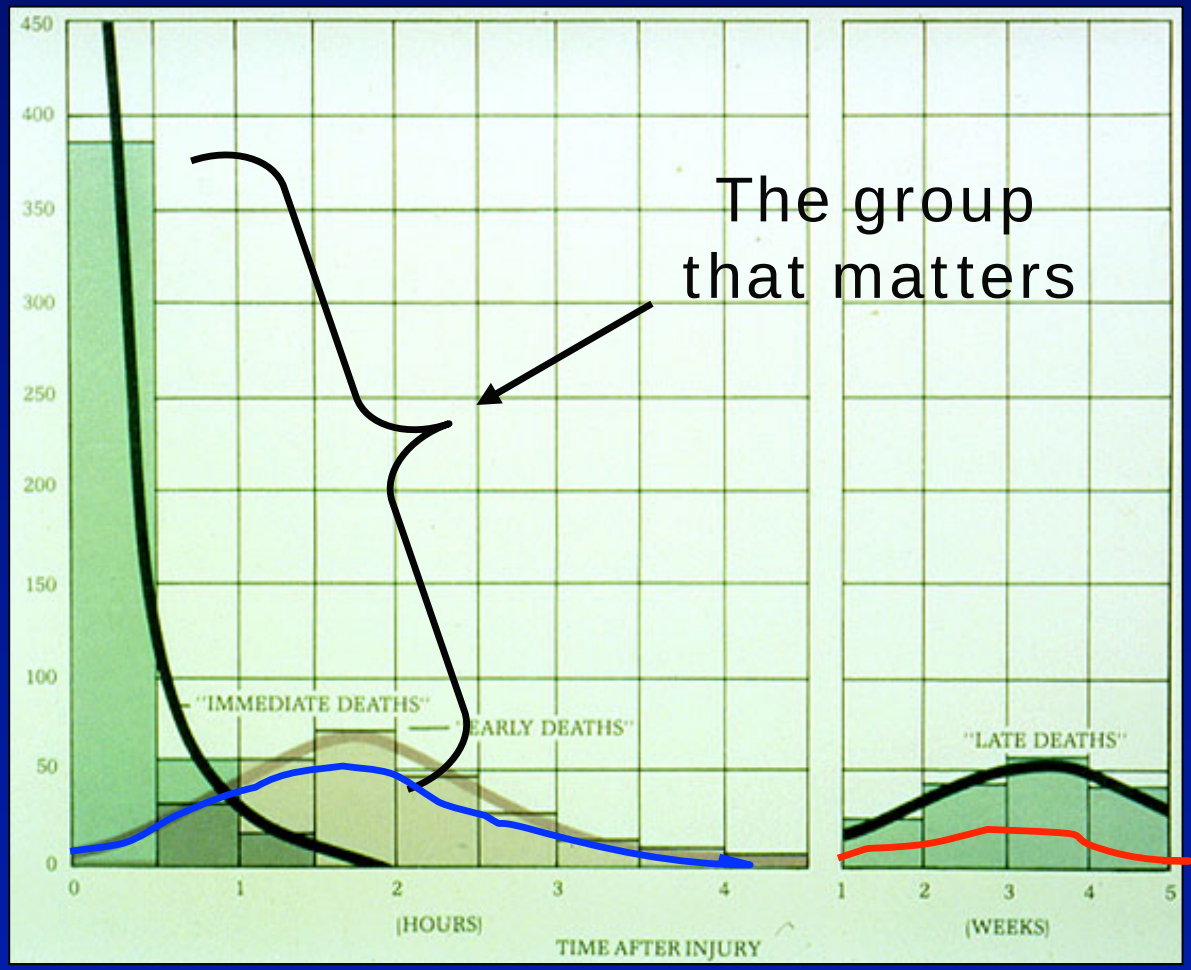
John Kirkpatrick, MD

- Scientific inquiry
- Writing clearly
- Being a good mentor
- Importance of funding

Area of Investigation

Early Trauma Care

The Trimodal Distribution Of Trauma Deaths



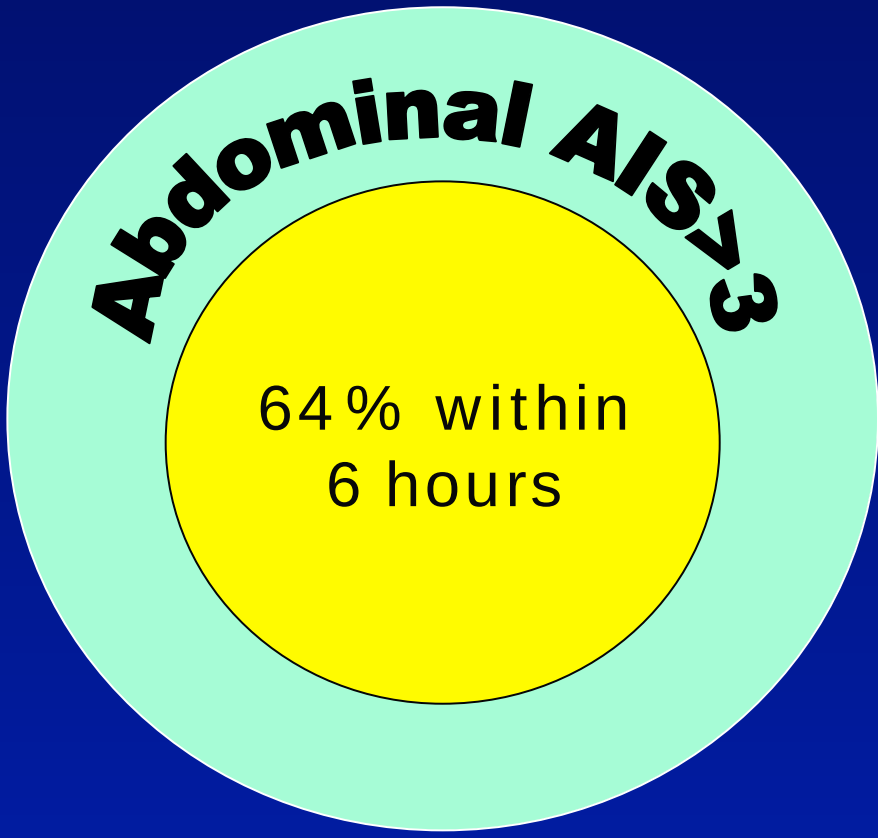
The Trimodal Distribution of Trauma Deaths

- Within the first 6 hours:
  75% of penetrating deaths

  Velmahos, J Trauma, 2004

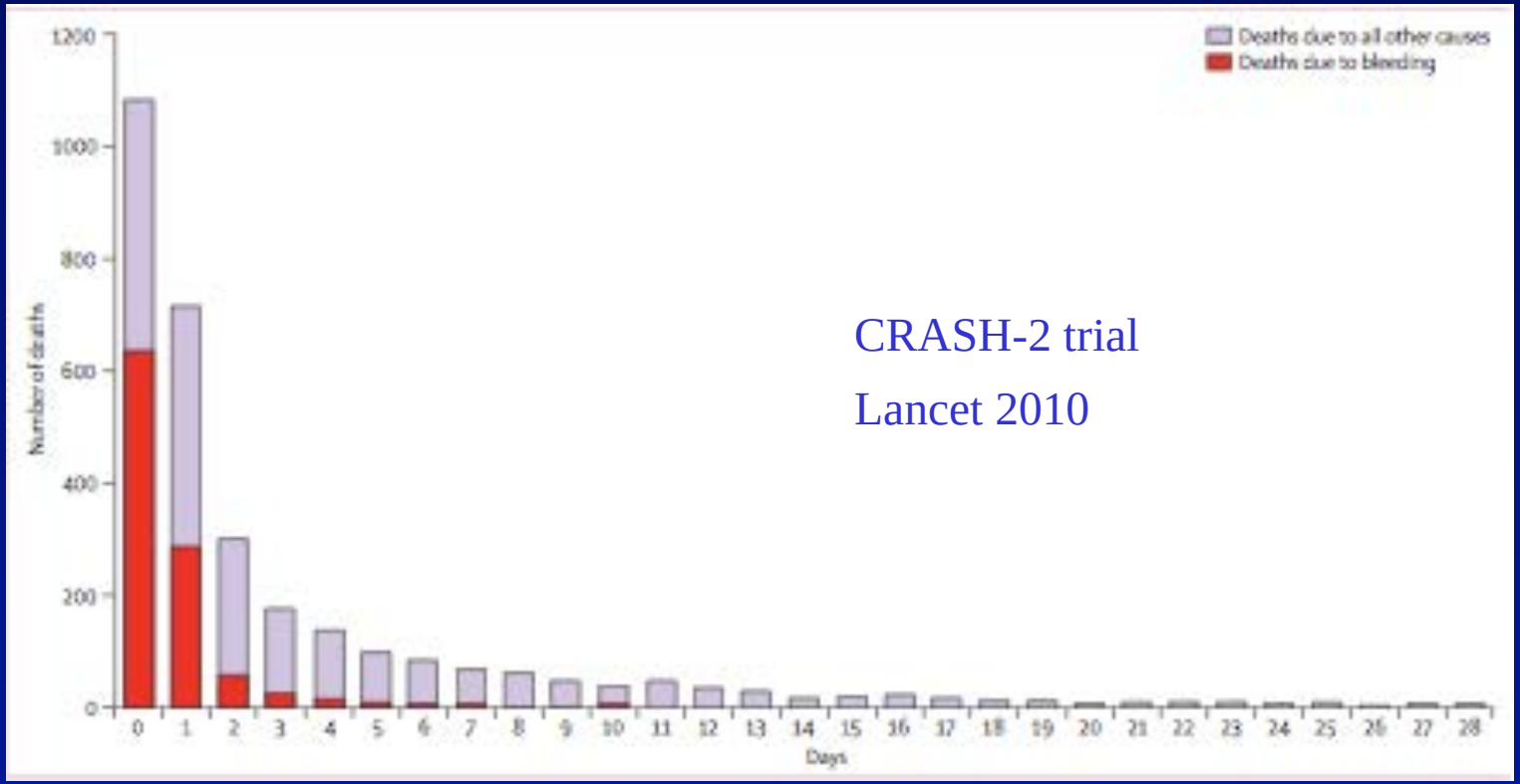
- Within the first 3 hours:
  54% of blunt trauma deaths

  Marson, J Trauma, 2001



Velmahos et al,
J Trauma 2004

Today: trauma deaths



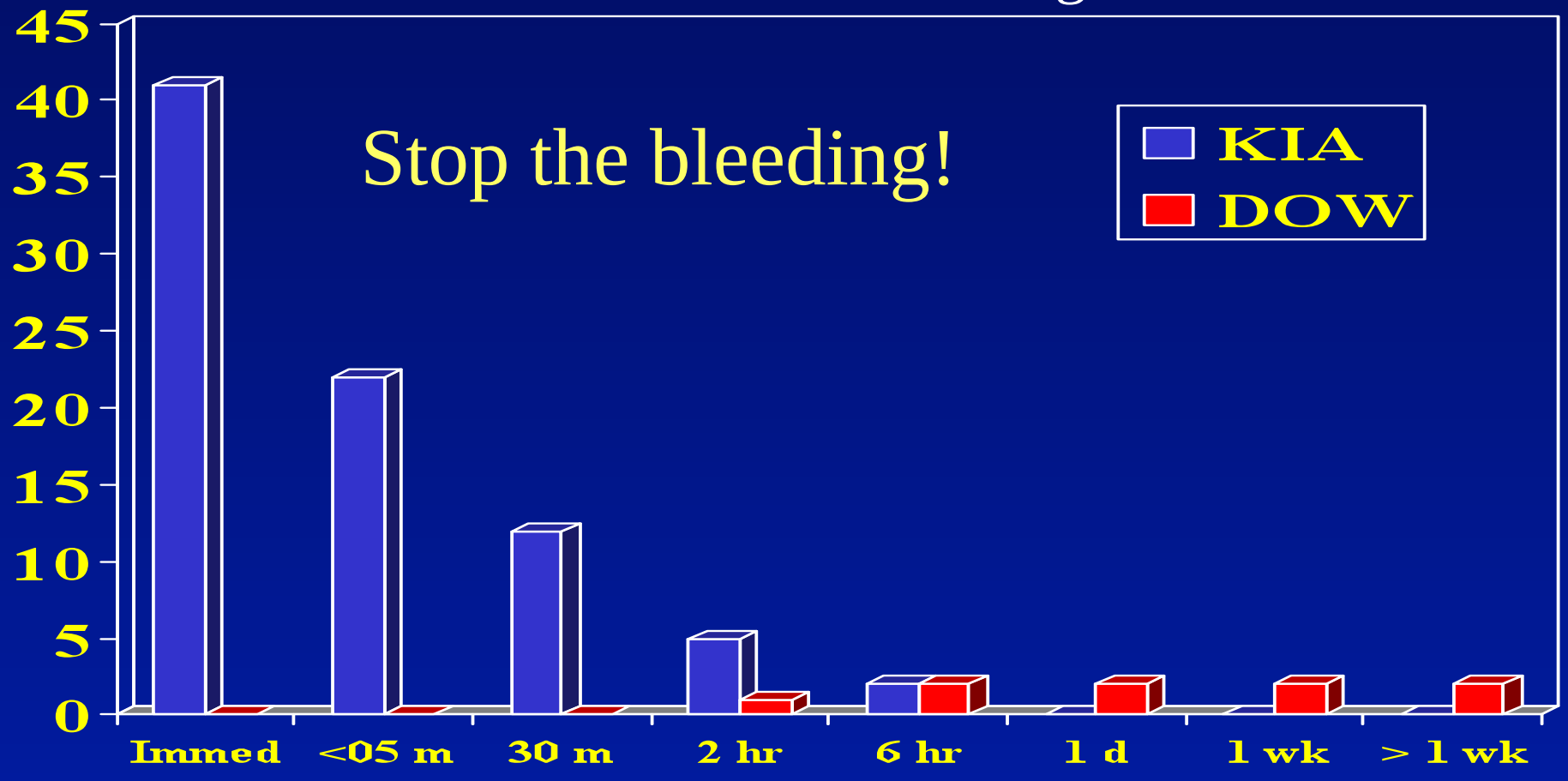
CRASH-2 trial

Lancet 2010

- RCT- 274 hospital, 40 countries, >20K patients
- Most died on the day of randomization
- Deaths due to MOF <2.5%

Percentage of Total Combat Deaths

Time from Wounding



Bellamy Anes & Periop Care of Combat Cas

Goals of early trauma care

- Keep alive
- Minimize organ injury
- Decrease bleeding

- Keep alive
- Preserve key organs
- ABC's

- Fix injuries
- Resuscitate
- Support organs

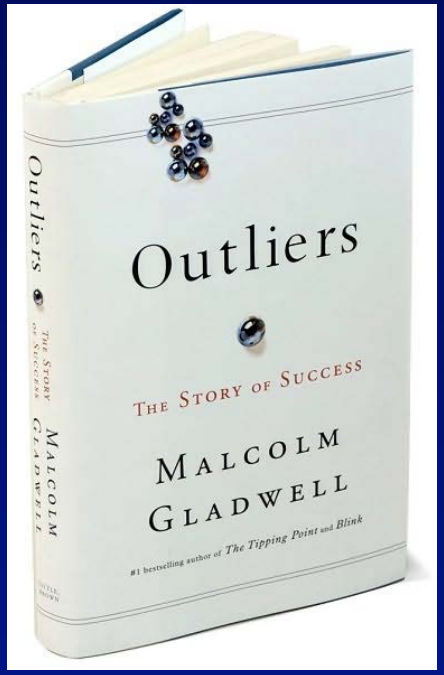
Pre-hospital → **ED** → **OR/SICU**

Hemorrhage Control

First you must stop the bleeding….

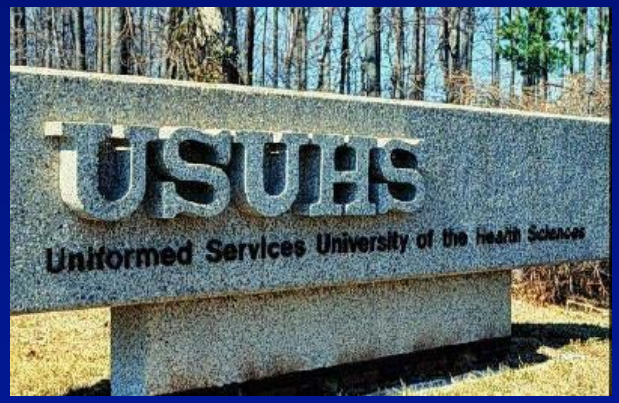
Success = talent + hard work

+ opportunity



June 1999: “Why don’t you work with me?” - Peter Rhee

First job


USUHS
Uniformed Services University of the Health Sciences


THE UNIFORMED SERVICES UNIVERSITY
OF THE HEALTH SCIENCES

A year of sharing an office with Peter

- **Challenge the dogma**
- **Innovative solutions for common problems**
- **Share credit**
- **Promote team members**
- **Military funding system**

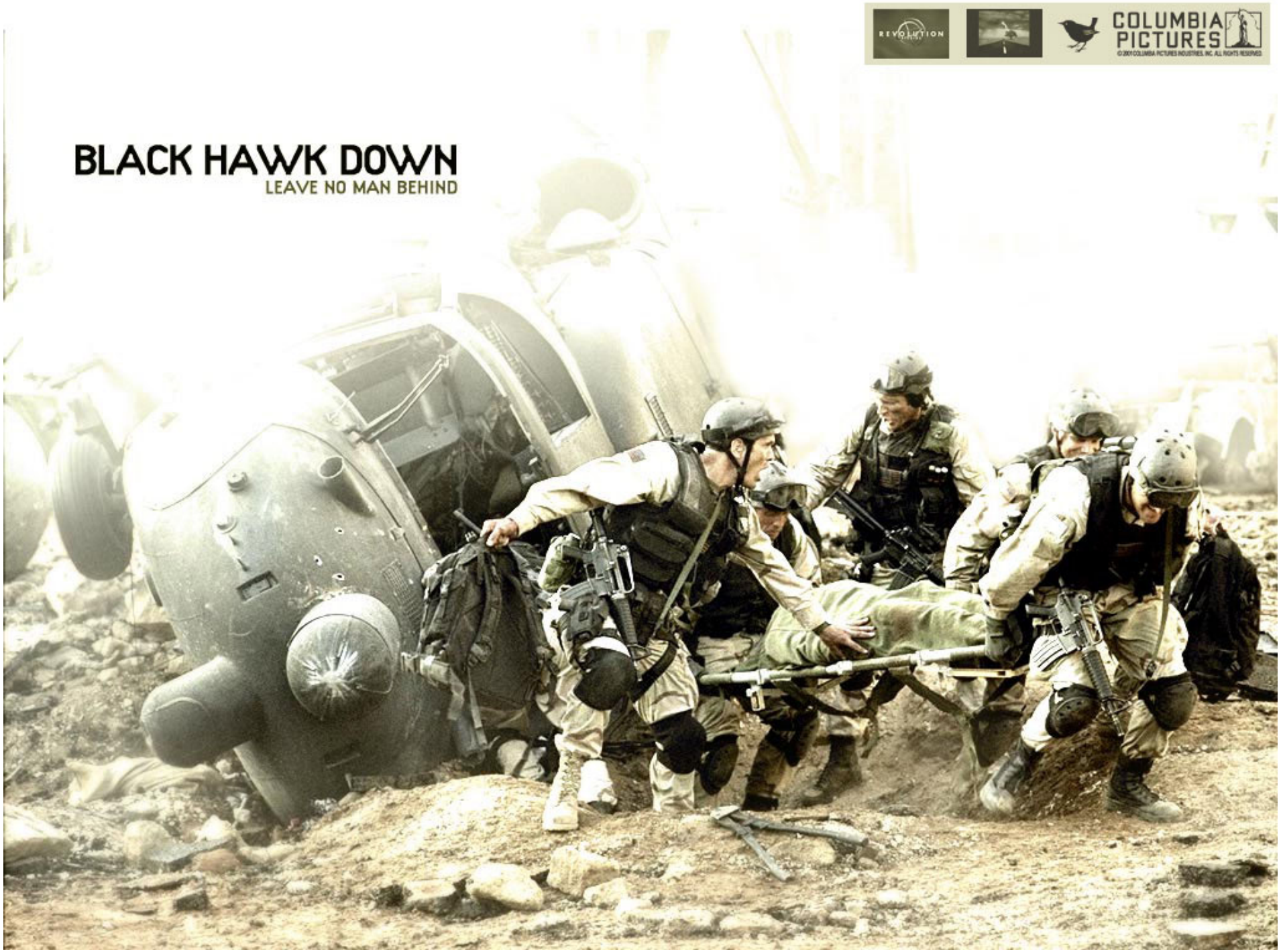
Alam HB and Rhee P = 40 manuscripts + 3 grants + 1 patent

Big decisions- Early 2001

- Married
- Smaller salary- more discretionary time
- Develop a research focus
- Grant writing:
  - Forward Treatment of Hemorrhagic Shock- ONR. $1,728,488.00
  - Induced Hypothermic Arrest in Traumatic Shock . RO1 HL71698- $1,482,000.00

Sept 2001

- " Can you find a new hemostatic dressing"
- "Need it now"


BLACK HAWK DOWN
LEAVE NO MAN BEHIND
REVOLUTION
COLUMBIA PICTURES

J Trauma. 2003;54:1077–1082.

The Journal of TRAUMA® Injury, Infection, and Critical Care

Comparative Analysis of Hemostatic Agents in a Swine Model of Lethal Groin Injury

Hasan B. Alam, MD, Gemma B. Uy, MD, Dana Miller, MD, Elena Koustova, PhD, Timothy Hancock, BS, Ryan Inocencio, BS, Daniel Anderson, BS, Orlando Llorente, MD, and Peter Rhee, MD, MPH

QuikClot improved survival to 100%. Wound temp 44 C


GETTY IMAGES
DHARB-I-MUMIN
The Frontier Post
Statesman
US attacks targets in Afghanistan
The Nation
US launches attack on Afghanistan
THE NEWS
US, allies attack Afghanistan
DAWN
The attack has begun
Osama vows no peace for 'infidel' America


COURAGE


WEAPON OF MASS DESTRUCTION


MARCH 31, 2003
www.time.com AOL Keyword: TIME
SPECIAL ISSUE
TIME
GULF WAR II
BAGHDAD
MARCH 21, 2003

MILITARY MEDICINE, 170, 1:63, 2005

Hemorrhage Control in the Battlefield: Role of New Hemostatic Agents

Guarantor: Hasan B. Alam, MD FACS
Contributors: Hasan B. Alam, MD*†; COL David Burris, MC USA*; LCDR Joseph A. DaCorta, MHA MSC USN (Ret.)‡; CDR Peter Rhee, MC USN*§

The New York Times

SUNDAY, MARCH 30, 2003

MILITARY MEDICINE

Armed With New Tools and Tactics, Doctors Head to the Battle

By GINA KOLATA

From redesigned first-aid kits to a radically new kind of surgery on the front lines, battlefield medicine has changed markedly and, as a result, doctors in the war in Iraq hope to significantly reduce the death rate from battlefield wounds — a rate that has not budged for 150 years.

Since the Civil War, experts in military medicine say, one of five wounded soldiers has died, half from profuse bleeding. Pentagon doctors hope to change that, and have mobilized an array of innovations.

Some, like putting pressure bandages in first-aid kits, are drugstore cheap. Others, like a new anticlotting drug for internal bleeding, are high-tech expensive, about $7,000 per dose. And some, like sending radically redesigned surgical teams to operate at the front lines, involve tactics and equipment that simply were not available in the last gulf war. These special surgery units were tested in Afghanistan, where they reduced the died-of-wounds rate, the death rate for those who survived long enough for a surgeon to operate, to a fraction of a percent. For the past half-century, it has hovered around 2 percent.

Doctors said it was hard to overestimate the difference.

There was little change from Vietnam to the first gulf war in doctors' instruments, drugs, techniques or tactics. Except for some in the Army, which put surgeons in the front lines in Desert Storm, wounded soldiers received first aid from medics but no surgical care until they were evacuated to a larger hospital.

Now, all the services have small mobile surgical teams scattered throughout the battlefield, where they operate on the most severely wounded as close to the front as possible. They do the minimum oper-

The substance was tested for battlefield use by Dr. Hasan Alam, a trauma surgeon at the Uniformed Services University of the Health Sciences in Bethesda, Md. Dr. Alam said he was haunted by troops who bled to death in Somalia before surgeons could help them.

For Dr. Alam, it meant that "your buddy has to stop the bleeding, not the medic, not the surgeon."

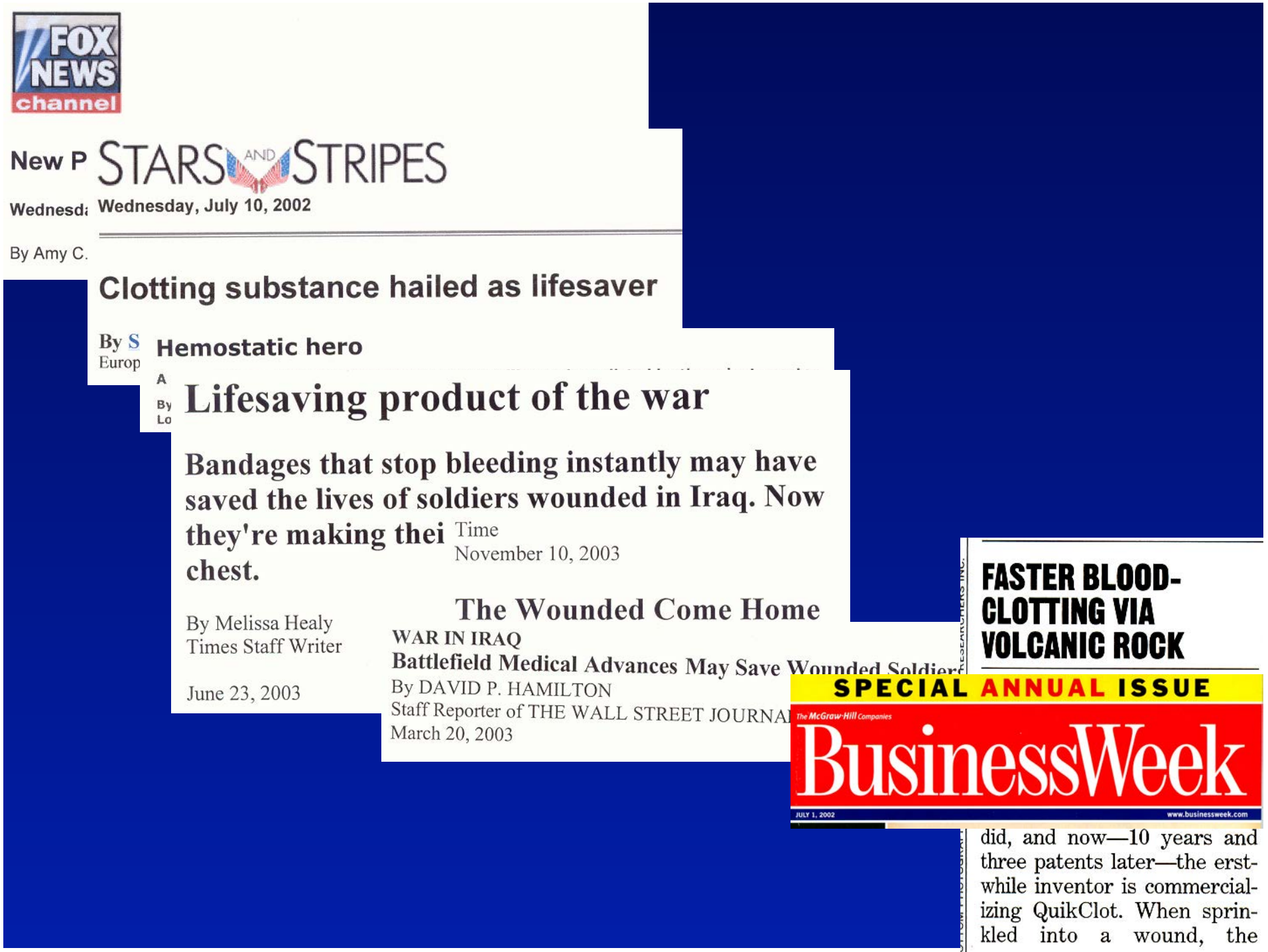
So he turned to QuikClot, a product made of the mineral zeolite and sold over the counter by Z-Medica. It looks like cat litter but, sprinkled on a wound, it absorbs water from blood, concentrating the body's own clotting factors and speeding up the formation of a clot.

Z-Medica has supplied 50,000 doses to the military.

Dr. Alam and his colleagues tested the substance on 36 Yorkshire swine, which are close to a person's size. The results have not been published, but Dr. Alam said QuikClot converted wounds that were 100 percent fatal into wounds that were 100 percent nonfatal — clots formed and none of the animals died.

Although the Marine Corps plans to use it, other branches of the military are not yet convinced. The question is whether to use it, and at what dose. One concern is that heat is generated when QuikClot is poured on a wound, and the fear is that it might burn tissue. "We don't have a huge amount of data," Dr. Alam said. "We've done two studies."

Also, the troops must be trained in how to use it and surgeons must be


FOX NEWS channel
New P
STARS AND STRIPES
Wednesda
Wednesday, July 10, 2002
By Amy C.
Clotting substance hailed as lifesaver
By S
Europ
Hemostatic hero
A
By
Lo
Lifesaving product of the war
Bandages that stop bleeding instantly may have saved the lives of soldiers wounded in Iraq. Now they're making thei
chest.
By Melissa Healy
Times Staff Writer
June 23, 2003
Time
November 10, 2003
The Wounded Come Home
WAR IN IRAQ
Battlefield Medical Advances May Save Wounded Soldier
By DAVID P. HAMILTON
Staff Reporter of THE WALL STREET JOURNA
March 20, 2003
FASTER BLOOD-CLOTTING VIA VOLCANIC ROCK
SPECIAL ANNUAL ISSUE
The McGraw-Hill Companies
BusinessWeek
JULY 1, 2002
www.businessweek.com
did, and now—10 years and three patents later—the erst-while inventor is commercial-izing QuikClot. When sprin-kled into a wound, the

Z-MEDICA
Products for Hemostasis

QUIKCLOT EVALUATION SHEET

(Please print and answer all questions possible. Answers will not be released to the public without written specific authorization.)

Name: Jeroms Taylor, MD Title: Battalion Surgeon / 2nd MARINE DIVISION

Company/Organization: Currently: Light Armored Reconnaissance / Formerly: 2nd Battalion 8th Marines

Address: Camp Lejeune, NC

City, State, Zip: 3AA Country: USA

Phone: 910-451-5987 ~~Fax:~~ Email: taylorjd3e 2mardiv.usmc.mil

PLEASE DESCRIBE YOUR USE OF QUIKCLOT: (attach additional sheets if necessary)

Date: ~~10/29/03.~~ March 2003 - July 2003 Location: Operation Iraqi Freedom

Description: I was the battalion surgeon for a Marine Infantry battalion during the start of OIF. While on the battlefield I treated ten casualties = Quick clot and without a doubt it prevented massive hemorrhage as well as loss of limbs. I recommend wide usage of this product.

Evaluation: Outstanding!

Any additional comments:

I agree that different sizes should be made available or some sort of re-sealable package

Signature: [signature] Date: 12/29/03

PLEASE RETURN TO ADDRESS BELOW, ATTENTION: JESSICA PERKINS

Z-MEDICA, LLC. 35 Budney Road, Newington, CT 06111 Phone: 860.667.2201 Fax: 860.667.2222 Web: www.z-medica.com Email: info@z-medica.com

Z-MEDICA
Products for Hemostasis

QUIKCLOT EVALUATION SHEET

(Please print and answer all questions possible. Answers will not be released to the public without written specific authorization.)

Name: Benoit David J Title: SGT

Company/Organization: U.S. Army

Address: 15354 Murphy St Apt A

City, State, Zip: FT Polk LA 71459 Country: USA

Phone: 337 531-5057 Fax: Email: david.benoit@us.army.mil

PLEASE DESCRIBE YOUR USE OF QUIKCLOT: (attach additional sheets if necessary)

Date: 24 May 03 Location: Baghdad Iraq

Description: Treat a gunshot wound (GSW) to right thigh. Patient was bleeding profusilly. Applied Quickclot. The bleeding stopped in returning saving the soldier's leg and life

Evaluation: I think this product is great. I am would recommending to superiors to keep product on hand

Any additional comments:

Signature: David J Benoit Date: 29 Oct 03

PLEASE RETURN TO ADDRESS BELOW, ATTENTION: JESSICA PERKINS

The greatest privilege is to make a difference.

Z-MEDICA, LLC, 35 Budney Road, Newington, CT 06111 Phone: 860.667.2201 Fax: 860.667.2222 Web: www.z-medica.com Email: info@z-medica.com

J Trauma. 2004;56:974–983.

The Journal of TRAUMA® Injury, Infection, and Critical Care

Application of a Zeolite Hemostatic Agent Achieves 100% Survival in a Lethal Model of Complex Groin Injury in Swine

Hasan B. Alam, MD, Zheng Chen, MD, PhD, Amin Jaskille, MD, Racel Ireneo Luis C. Querol, MD, Elena Koustova, PhD, Ryan Inocencio, BS, Richard Conran, MD, Adam Seufert, HS, Nanna Ariaban, BS, Kevin Toruno, BS, and Peter Rhee, MD, MPH

J Trauma. 2006;61:1312–1320.

The Journal of TRAUMA® Injury, Infection, and Critical Care

Testing of Modified Zeolite Hemostatic Dressings in a Large Animal Model of Lethal Groin Injury

Naresh Ahuja, MD, Todd A. Ostomel, PhD, Peter Rhee, MD, Galen D. Stucky, PhD, Richard Conran, MD, Zheng Chen, MD, PhD, Ghada A. Al-Mubarak, MD, George Velmahos, MD, Marc deMoya, MD, and Hasan B. Alam, MD

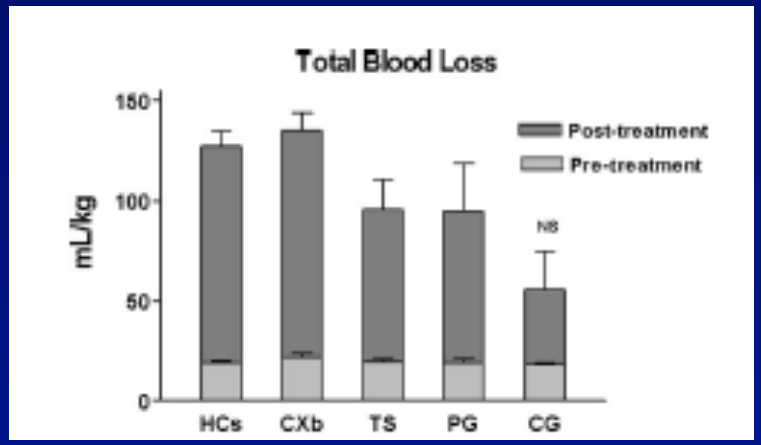
QuikClot Use in Trauma for Hemorrhage Control: Case Series of 103 Documented Uses

Peter Rhee, MD, MPH, Carlos Brown, MD, Matthew Martin, MD, Ali Salim, MD, Dave Plurad, MD, Donald Green, MD, Lowell Chambers, MD, Demetrios Demetriades, MD, PhD, George Velmahos, MD, and Hassan Alam, MD

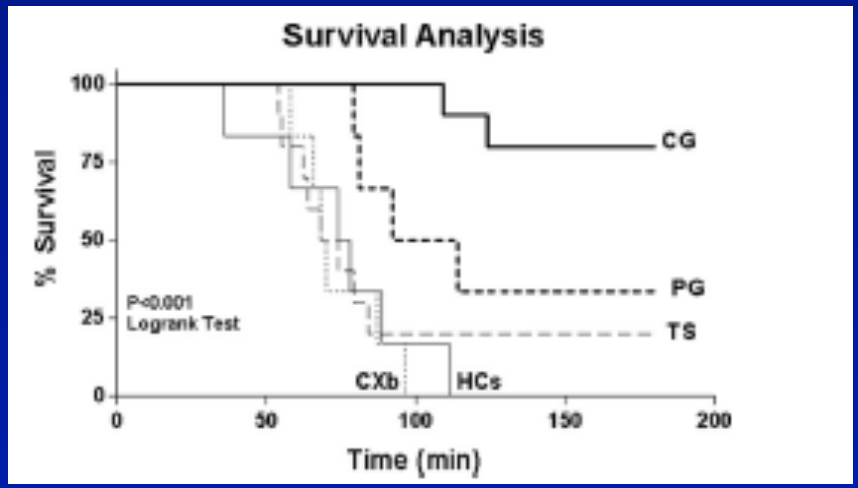
J Trauma 2008


HEY!
4-19
YOU STAY WITH ME, MAN - YOU HEAR ME?
MEDIC!
WE'RE GONNA GET YOU OUTA HERE! EVERYTHING'S GONNA BE COOL, MAN!
B.D.?
HEY!
HEY!
MEDEVAC EN-ROUTE!
YOU'RE NOT DYING HERE, MAN! NOT TODAY!
NEED SOME BEADS! AND A QUICK-CLOT! NOW!
HEAR ME? NOT TODAY!
RAY?
4-20
HIS B.P.'S STABLE! LET'S LOAD HIM!
RAY? WHAT'S GOING ON?
B.D.! STAY WITH ME, DAMMIT!
OKAY, RAY, I'LL STAY...
WHOP! WHOP!
I SAID NOT TODAY!
DRIP'S IN!
GET HIS HELMET OFF!
4-21
CAREFUL, YO!
90 OVER 60!
LET ME DO MY JOB, MAN...
GO, GO, GO!
ALMOST THERE, B.D.! EVERYTHING'S GOOD!
NOT YOUR TIME, BRO!
NOT TODAY!

2nd generation dressings



QuikClot Combat Gauze now recommended as first line of treatment




QuikClot
COMBAT
GAUZE
For Temporary External Use
To Control Traumatic Bleeding


CELOX GAUZE


CELOX
Haemostatic Granules
TEAR HERE
Medtrade
15g


Vacuum Packed - Sterile Product
QuikClot
Advanced Clotting Sponge
To Stop Moderate-to-Severe Bleeding
By Promoting Rapid Coagulation
FOR EMERGENCY EXTERNAL USE
DO NOT EAT
See Directions On Back


THIS SIDE UP
THIS SIDE UP
THIS SIDE UP

Lessons learned

- Take risks
- Think big
- **WRITE**

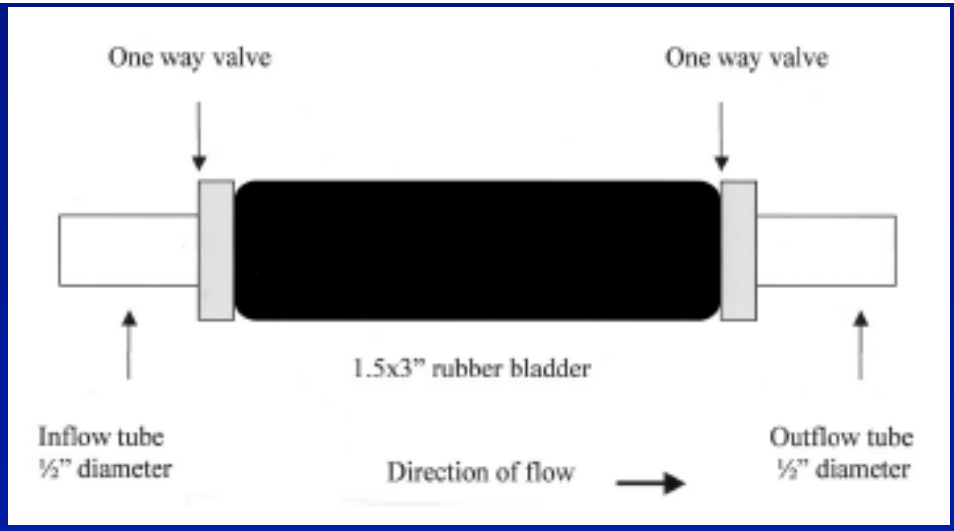
Biggest predictor of academic success = Ability to write Clearly, on Schedule, and Consistently

A word about intellectual property

A Portable Handpump Is Effective in the Evacuation of Hemothorax in a Swine Model of Penetrating Chest Injury

Amin Jaskille, MD, Peter Rhee, MD, MPH, Elena Koustova, PhD, Timothy Hancock, BS, Ryan Inocencio, BS, Troy A. Lewis, BS, Adam Seufert, HS, and Hasan B. Alam, MD

J Trauma. 2003;55:864–868.



WTA 2003- Earl Young Paper

US 20080091174A1

(19) **United States**

(12) **Patent Application Publication**

Alam et al.

(10) **Pub. No.: US 2008/0091174 A1**

(43) **Pub. Date: Apr. 17, 2008**

(54) **PORTABLE HAND PUMP FOR EVACUATION OF FLUIDS**

(75) Inventors: **Hasan B. Alam**, Natick, MA (US); **Peter Rhee**, San Gabriel, CA (US); **Emily Rhee**, San Gabriel, CA (US)

Correspondence Address:
STOEL RIVES LLP - SLC
201 SOUTH MAIN STREET, ONE UTAH CENTER
SALT LAKE CITY, UT 84111

(73) Assignees: **The Henry M. Jackson Foundation For The Advancement Of Military Medicine, Inc.**, Rockville, MD (US); **Uniformed Services University Of The Health Sciences**, Bethesda, MD (US)

(21) Appl. No.: **10/595,450**

(22) PCT Filed: **Nov. 22, 2004**

(86) PCT No.: **PCT/US04/38837**

§ 371 (c)(1),
(2), (4) Date: **Jun. 21, 2007**

Related U.S. Application Data

(60) Provisional application No. 60/523,321, filed on Nov. 20, 2003.

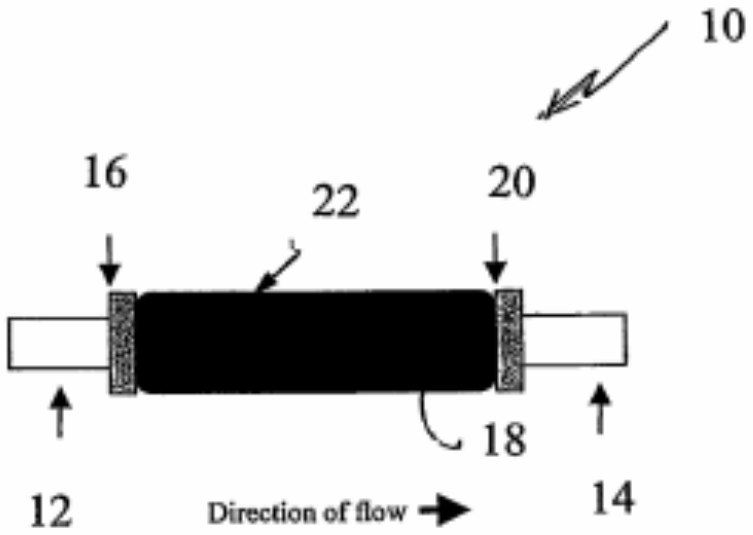
Publication Classification

(51) **Int. Cl.**
A61M 1/00 (2006.01)

(52) **U.S. Cl.** **604/541**

(57) **ABSTRACT**

A manually operable pump for the effective removal of fluids to include blood, blood clots, fluid, and air from a body cavity of a subject is provided. The manually operable pump is adapted to be connect to a range of fluid conduits and is equipped with one-way valves that effectively permit flow of fluid through the pump in only one direction. The sensitivity of the one-way valves is such that when properly positioned, fluid can flow through the valves and out of the pump without manual compression of the pump and with the aid of gravity power alone.



BARD ACCESS SYSTEMS

SEARCH

PRODUCTS | RESOURCES | EDUCATION | PATIENTS | PROGRAMS | CATALOG

DRAINAGE DEVICES

ASPIRA* PLEURAL DRAINAGE

- OVERVIEW
- FEATURES
- SPECIFICATIONS
- ACCESSORIES
- KIT COMPONENTS
- RESOURCES

- SAFETY INFORMATION

- WWW.MYASPIRA.COM
- PRODUCT CATALOG
- SALES CONTACT

Aspira PLEURAL DRAINAGE SYSTEM

FEATURES

Compassionate Treatment for Malignant Pleural Effusion Patients

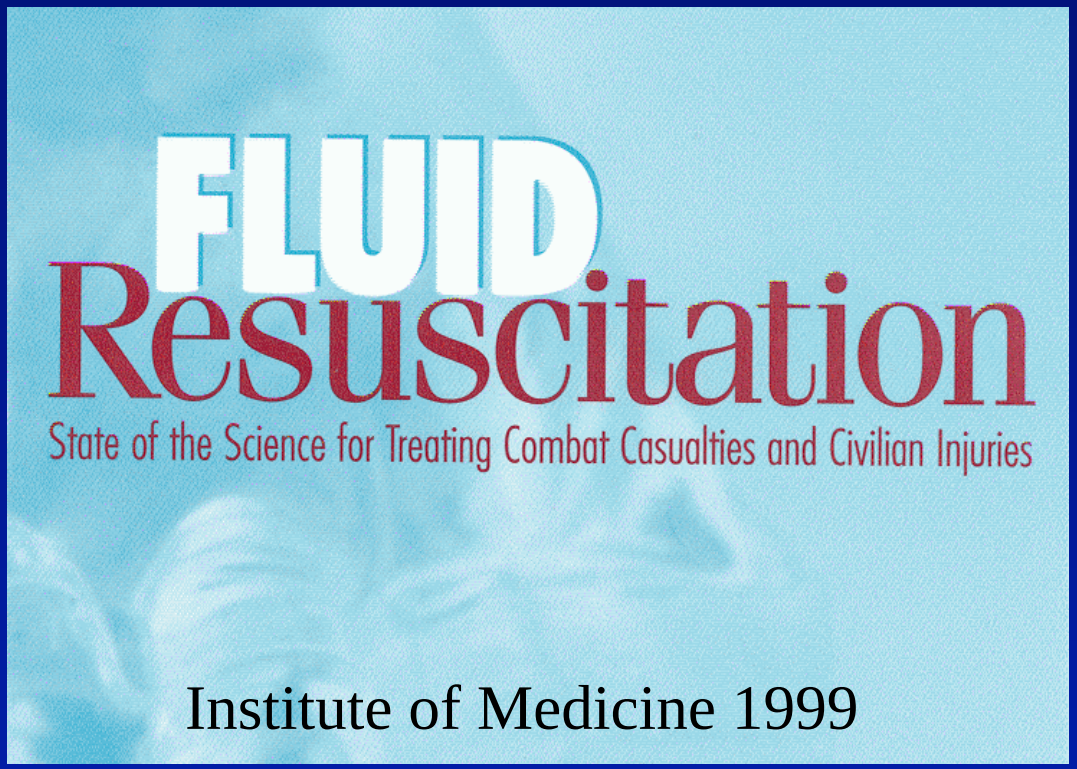
The Aspira* Pleural Drainage Catheter is a tunneled, long-term catheter used to drain accumulated fluid from the pleural cavity to relieve symptoms associated with malignant pleural effusion and other recurrent pleural effusions.

The Aspira* Pleural Drainage Catheter is easy to insert and the

30 Million devices manufactured

Resuscitation

Aggressive fluid resuscitation for bleeding trauma patient: Good or bad?



Institute of Medicine 1999

Impact of Resuscitation fluids on Cellular Functions

ELSEVIER

Resuscitation xxx (2004) xxx–xxx

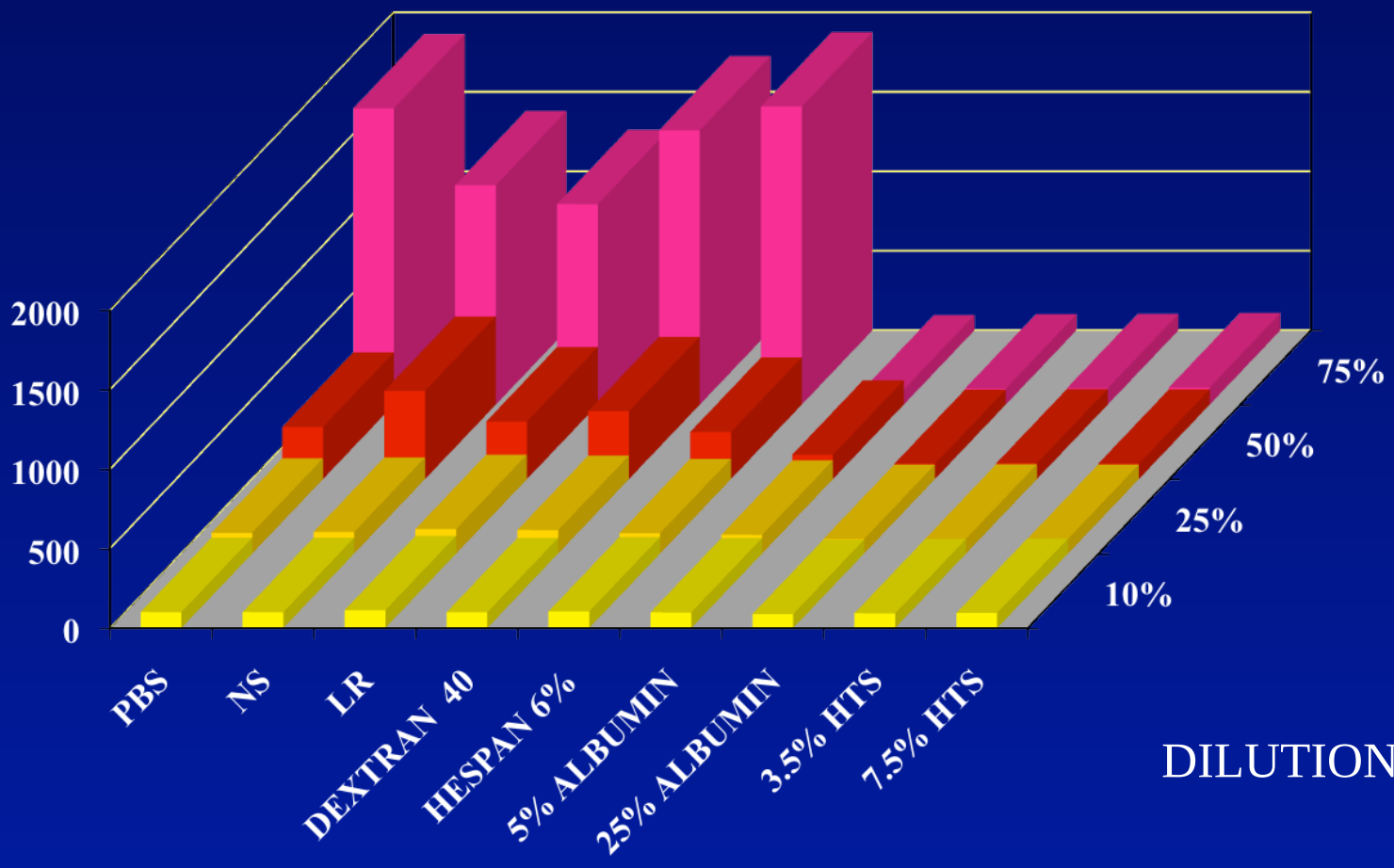
RESUSCITATION

www.elsevier.com/locate/resuscitation

Effect of different resuscitation strategies on neutrophil activation in a swine model of hemorrhagic shock

Hasan B. Alam [a,b,*], Kathleen Stanton [a], Elena Koustova [a], David Burris [a], Norman Rich [a], Peter Rhee [a,c]

NEUTROPHIL ACTIVATION

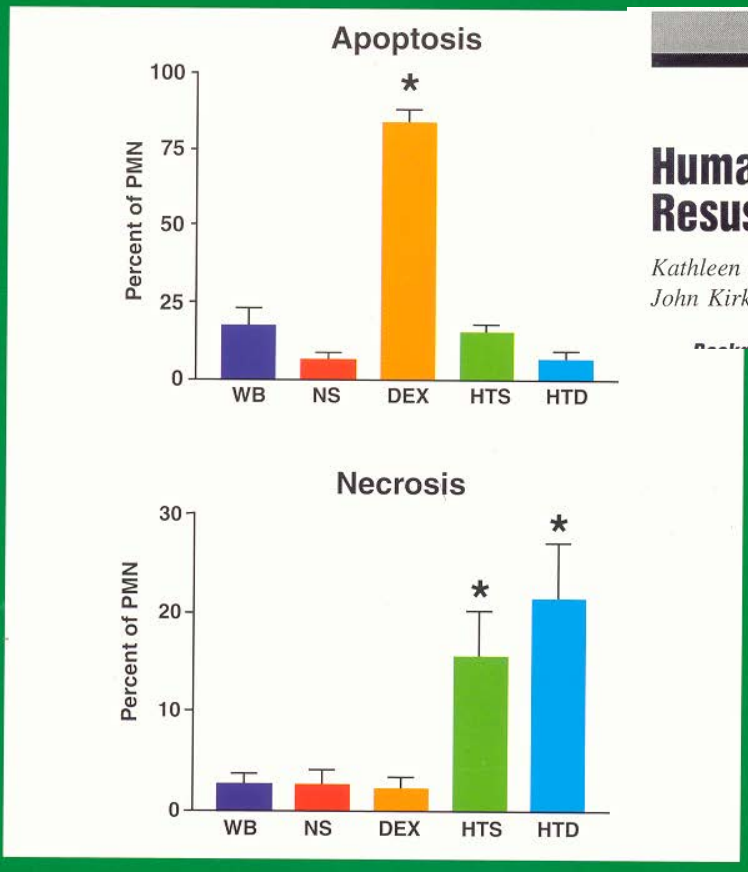


Rhee et al. Crit Care Med. 28:74-78, 2000.

Volume 54 ▪ Number 6 ▪ June 2003

The Journal of TRAUMA®

Injury, Infection, and Critical Care



Human Polymorphonuclear Cell Death after Exposure to Resuscitation Fluids In Vitro: Apoptosis versus Necrosis

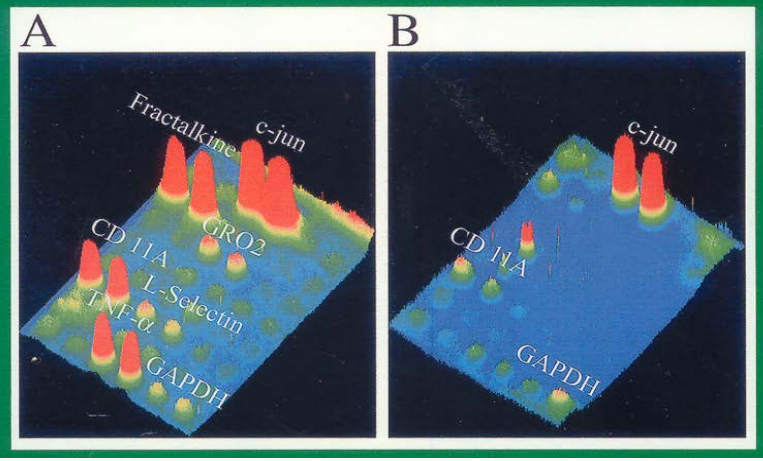
Kathleen Stanton, MS, Hasan B. Alam, MD, Peter Rhee, MD, MPH, Orlando Llorente, MD, John Kirkpatrick, MD, and Elena Koustova, PhD

Volume 52 ▪ Number 5 ▪ May 2002

The Journal of

TRAUMA®

Injury, Infection, and Critical Care



The Journal of **TRAUMA®** *Injury, Infection, and Critical Care*

Effects of Lactated Ringer's Solutions on Human Leukocytes

Elena Koustova, PhD, Kathleen Stanton, MS, Vadim Gushchin, MD, Hasan B. Alam, MD, Svetlana Stegalkina, MS, and Peter M. Rhee, MD, MPH

The Journal of TRAUMA® Injury, Infection, and Critical Care

J Trauma. 2002;52:867–871.

Cytokine Expression Profiling in Human Leukocytes after Exposure to Hypertonic and Isotonic Fluids

Vadim Gushchin, MD, Svetlana Stegalkina, MS, Hasan B. Alam, MD, John R. Kirkpatrick, MD, Peter M. Rhee, MD, MPH, and Elena Koustova, PhD

cDNA Profiling in Leukocytes Exposed to Hypertonic Resuscitation Fluids

J Am Coll Surg 2003;197:426-432

Vadim Gushchin, MD, Hasan B Alam, MD, FACS, Peter Rhee, MD, MPH, FACS, John R Kirkpatrick, MD, FACS, Elena Koustova, PhD

Resuscitation-Induced Pulmonary Apoptosis and Intracellular Adhesion Molecule-1 Expression in Rats Are Attenuated by the Use of Ketone Ringer's Solution

J Am Coll Surg Vol. 193, No. 3, September 2001

Hasan B Alam, MD, Brenda Austin, BS, Elena Koustova, PhD, Peter Rhee, MD, MPH, FACS

Ketone and pyruvate Ringer's solutions decrease pulmonary apoptosis in a rat model of severe hemorrhagic shock and resuscitation

Elena Koustova, PhD, Peter Rhee, MD, MPH, Timothy Hancock, BS, Huazhen Chen, MD, Ryan Inocencio, BS, Amin Jaskille, MD, William Hanes, BA, C. Robert Valeri, MD, *and* **Hasan B. Alam, MD,** *Bethesda, Md; Los Angeles, Calif; Boston, Mass; Washington, DC*

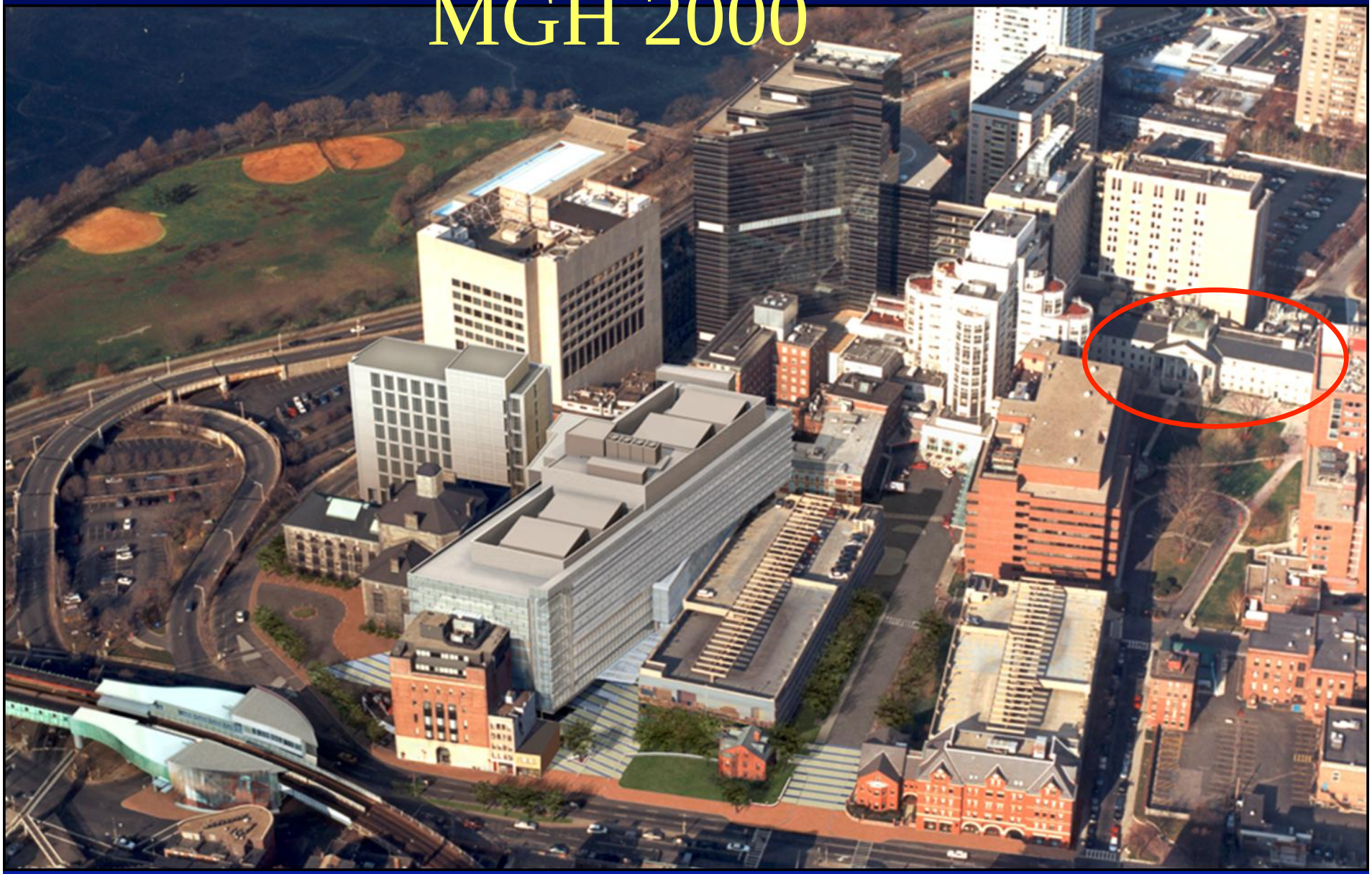
Surgery
August 2003

- Elimination of D-lactate decreases apoptotic cell death

MGH and Harvard Med School 1820s

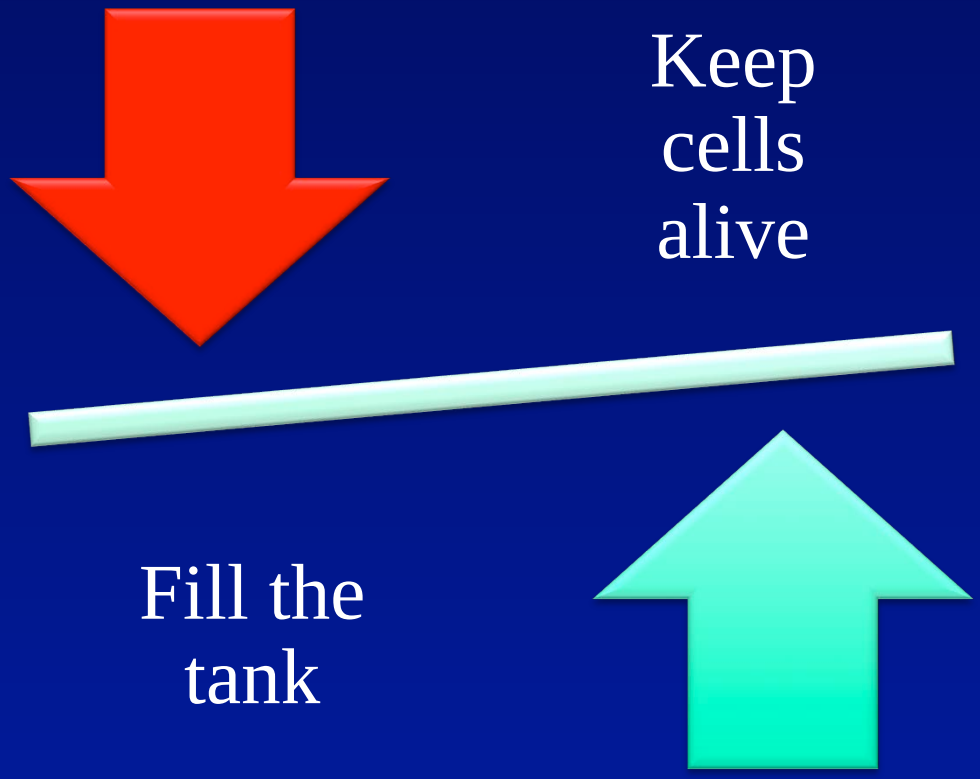
Harvard Medical School today

MGH 2000



Making survivors out of non-survivors

Surviving Blood Loss (SBL) Program



Alam HB, Velmahos GC. New trends in resuscitation. *Curr Probl Surg*. 2011;48(8):531-64

ELSEVIER

Resuscitation 54 (2002) 195–206

RESUSCITATION

www.elsevier.com/locate/resuscitation

cDNA array analysis of gene expression following hemorrhagic shock and resuscitation in rats

Hasan B. Alam [a,b,*,1], Svetlana Stegalkina [a,1], Peter Rhee [a,c], Elena Koustova [a]

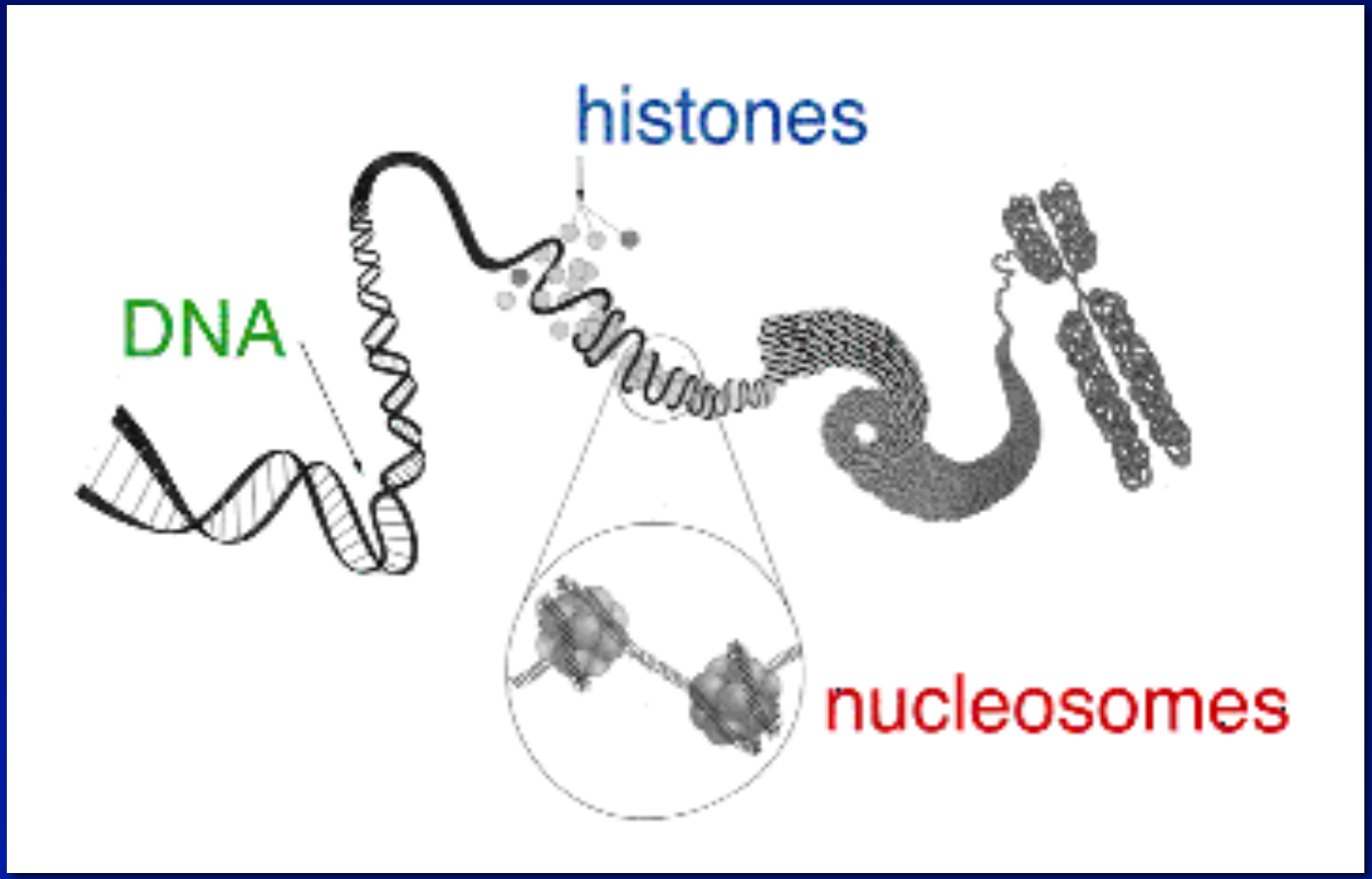
[a] *Departments of Surgery, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814, USA*
[b] *Washington Hospital Center, Washington, DC, USA*
[c] *The Naval Medical Center, San Diego, DC, USA*

Identification of Expression Patterns Associated with Hemorrhage and Resuscitation: Integrated Approach to Data Analysis

J Trauma. 2006;60:701–724.

Huazhen Chen, MD, Hasan B. Alam, MD, Racel Ireneo Luis C. Querol, MD, Peter Rhee, MD, Yongqing Li, MD, PhD, and Elena Koustova, PhD

Epigenetic regulation



Acetylation

- Controlled by two enzyme systems:

Histone acetyltransferase (HAT) - ↑ transcription
Histone deacetylase (HDAC) - ↓ transcription

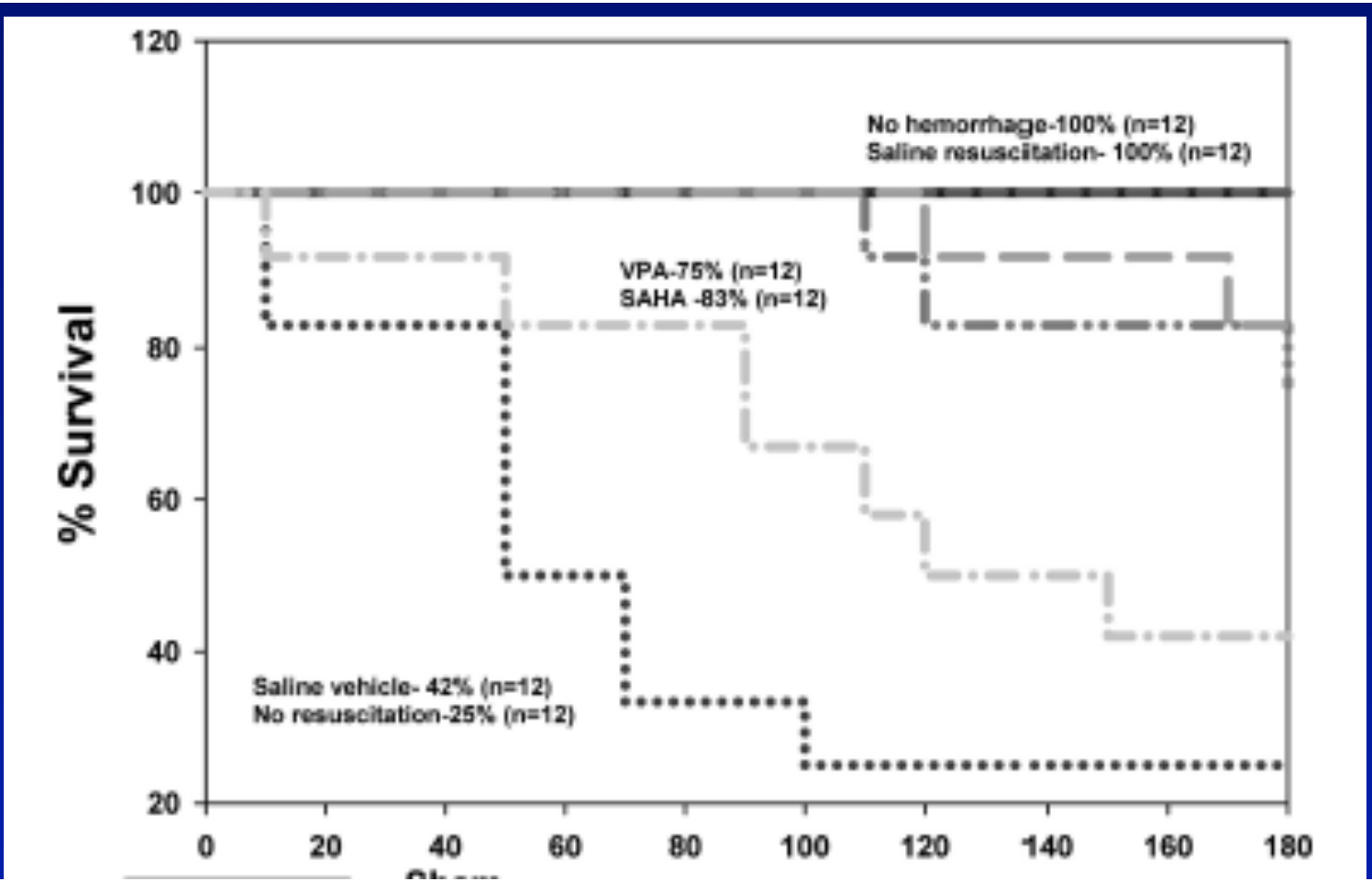
- Histone Deacetylase Inhibitors (HDACI- ↑ acetylation
  - Nuclear histones= ↑ transcription
  - Cytoplasmic proteins= altered function

The Journal of TRAUMA® Injury, Infection, and Critical Care

Surviving Blood Loss Without Fluid Resuscitation

Christian Shults, MD, Elizabeth A. Sailhamer, MD, Yongqing Li, MD, PhD, Baoling Liu, MD, Malek Tabbara, MD, Muhammad Umar Butt, MD, Fahad Shuja, MD, Marc deM George Velmahos, MD, and Hasan B. Alam, MD

J Trauma. 2008;64:629–640.



The Journal of TRAUMA® Injury, Infection, and Critical Care

Prevention of Hypoxia-Induced Neuronal Apoptosis Through Histone Deacetylase Inhibition

Yongqing Li, MD, PhD, Zengqiang Yuan, MD, PhD, Baoling Liu, MD, Elizabeth A. Sailhamer, MD, Christian Shults, MD, George C. Velmahos, MD, Marc deMoya, MD, and Hasan B. Alam, MD

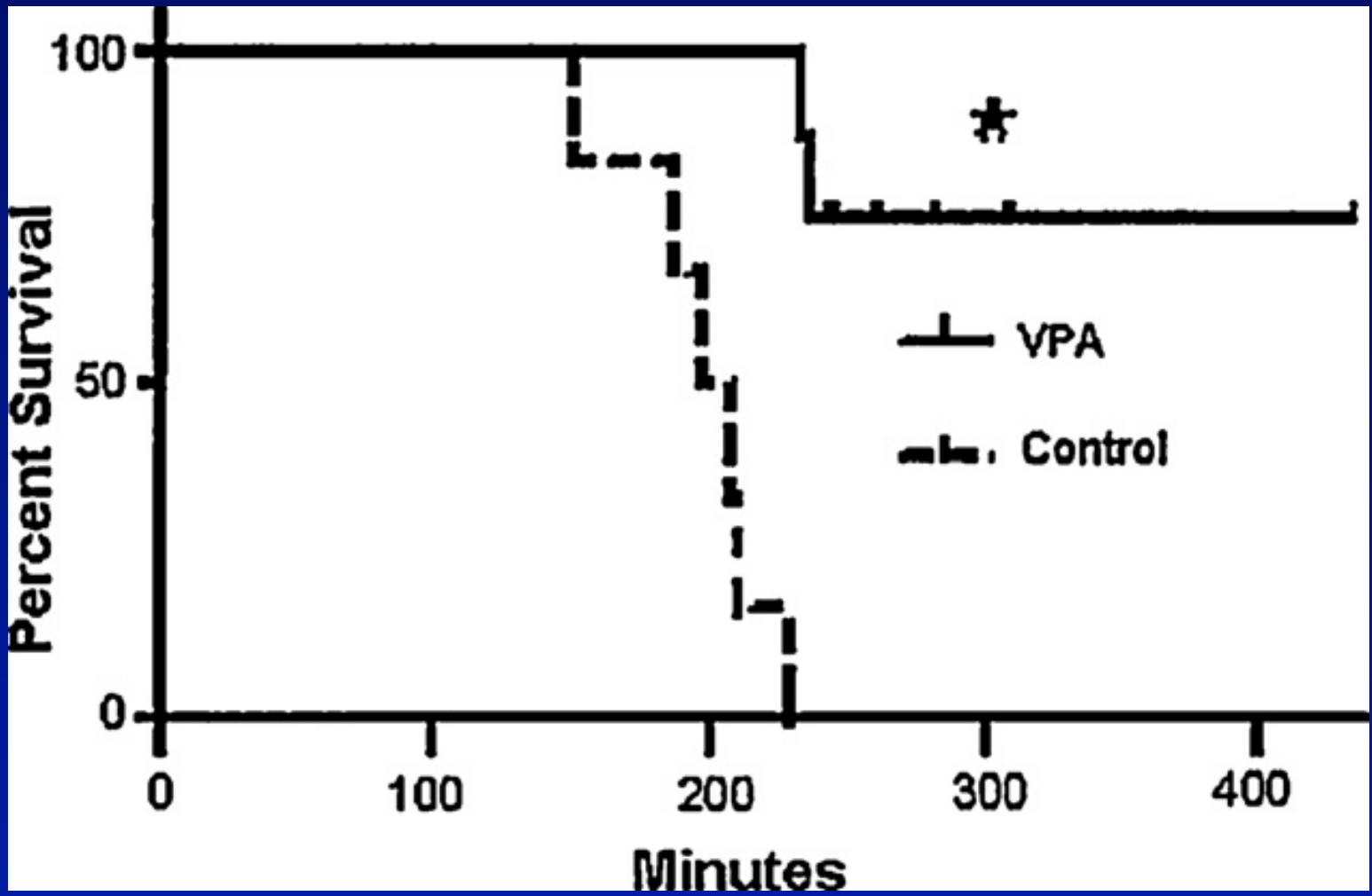
Is acetylation the new phosphorylation?

EMBO J 2000

Acetylation: a novel method for modulation of the immune response following trauma/hemorrhage and inflammatory second hit in animals and humans

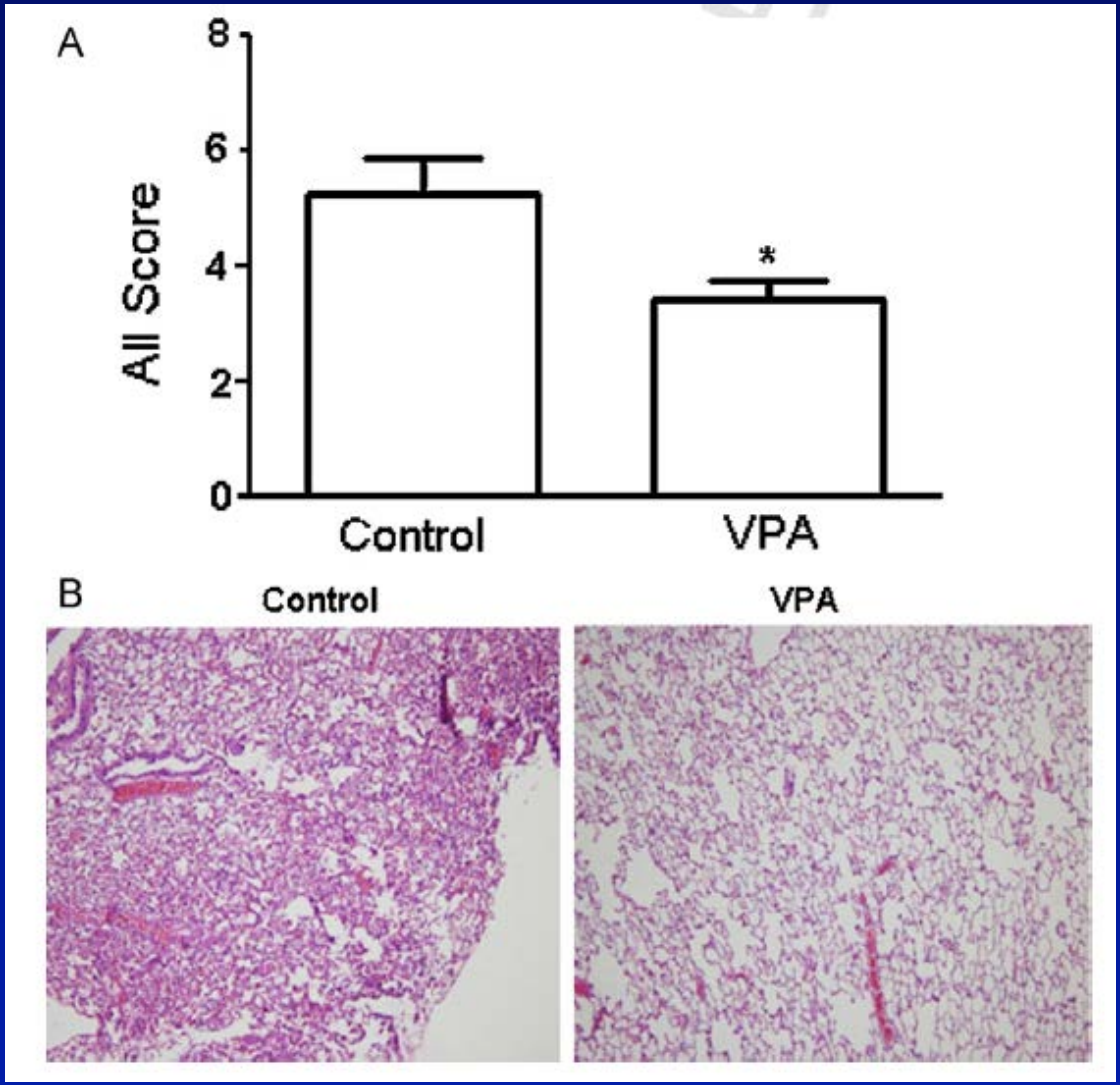
Elizabeth A. Sailhamer, MD,[a] Yongqing Li, MD, PhD,[a] Eleanor J. Smith,[a] Fahad Shuja, MD,[a] Christian Shults, MD,[a,c] Baoling Liu, MD,[a] Chad Soupir, MD,[b] Marc deMoya, MD,[a] George Velmahos, MD,[a] *and* **Hasan B. Alam, MD,[a]** *Boston, Mass and Washington, DC*

HDACI improve survival in intestinal ischemia-reperfusion



Resuscitation August 2011

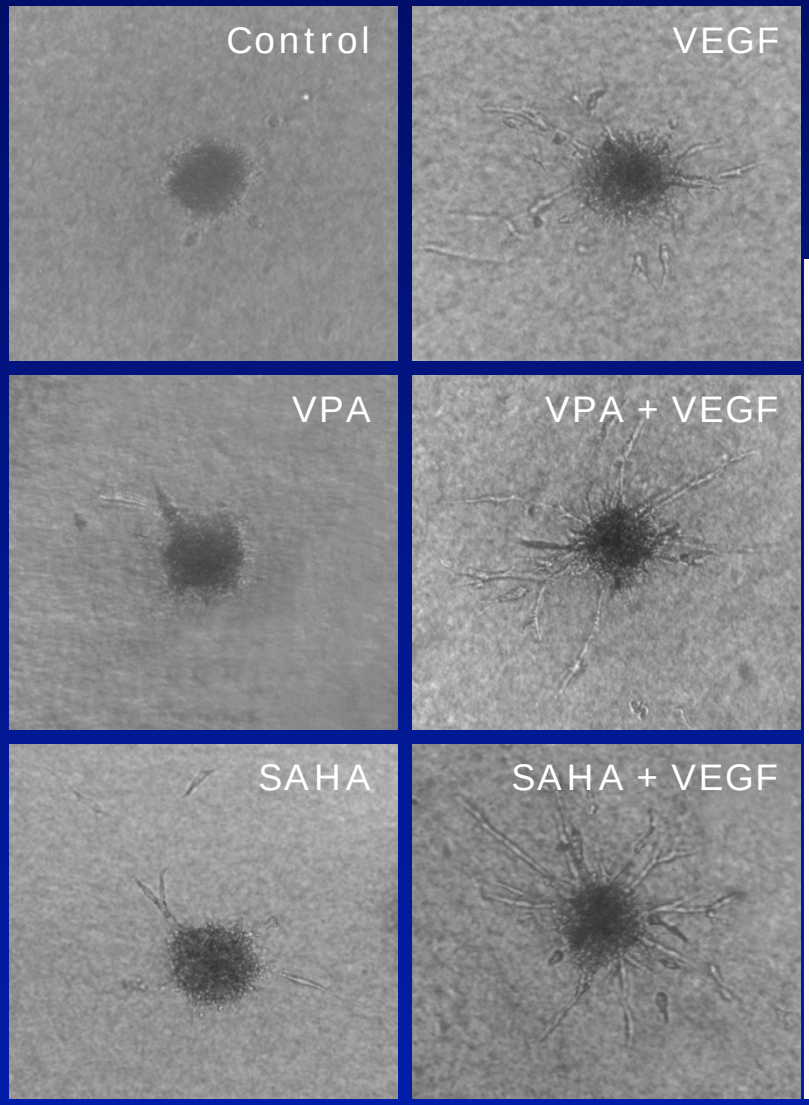
.. and decreased distant organ injury (ALI)

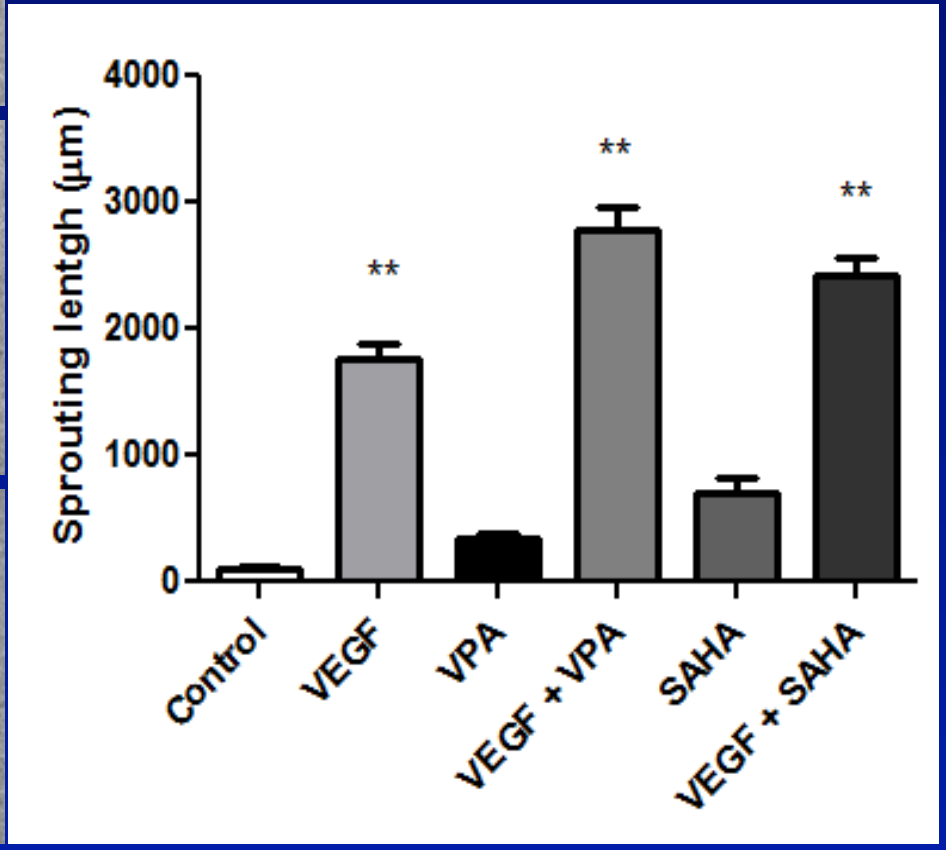


Histone deacetylase inhibitors enhance endothelial cell sprouting angiogenesis in vitro

Guang Jin, MD, PhD,[a] Dirk Bausch, MD,[b,c] Knightly Thomas, BS,[a] Zhengcai Liu, MD,[a] Yongqing Li, MD, PhD,[a] Baoling Liu, MD,[a] Jennifer Lu, BS,[a] Wei Chong, MD, PhD,[a] George Velmahos, MD, PhD,[a] *and* Hasan B. Alam, MD,[b] *Cambridge, Massachusetts, and Freiburg, Germany*

Surgery Sep 2011





Histone deacetylase inhibitor suberoylanilide hydroxamic acid attenuates Toll-like receptor 4 signaling in lipopolysaccharide-stimulated mouse macrophages

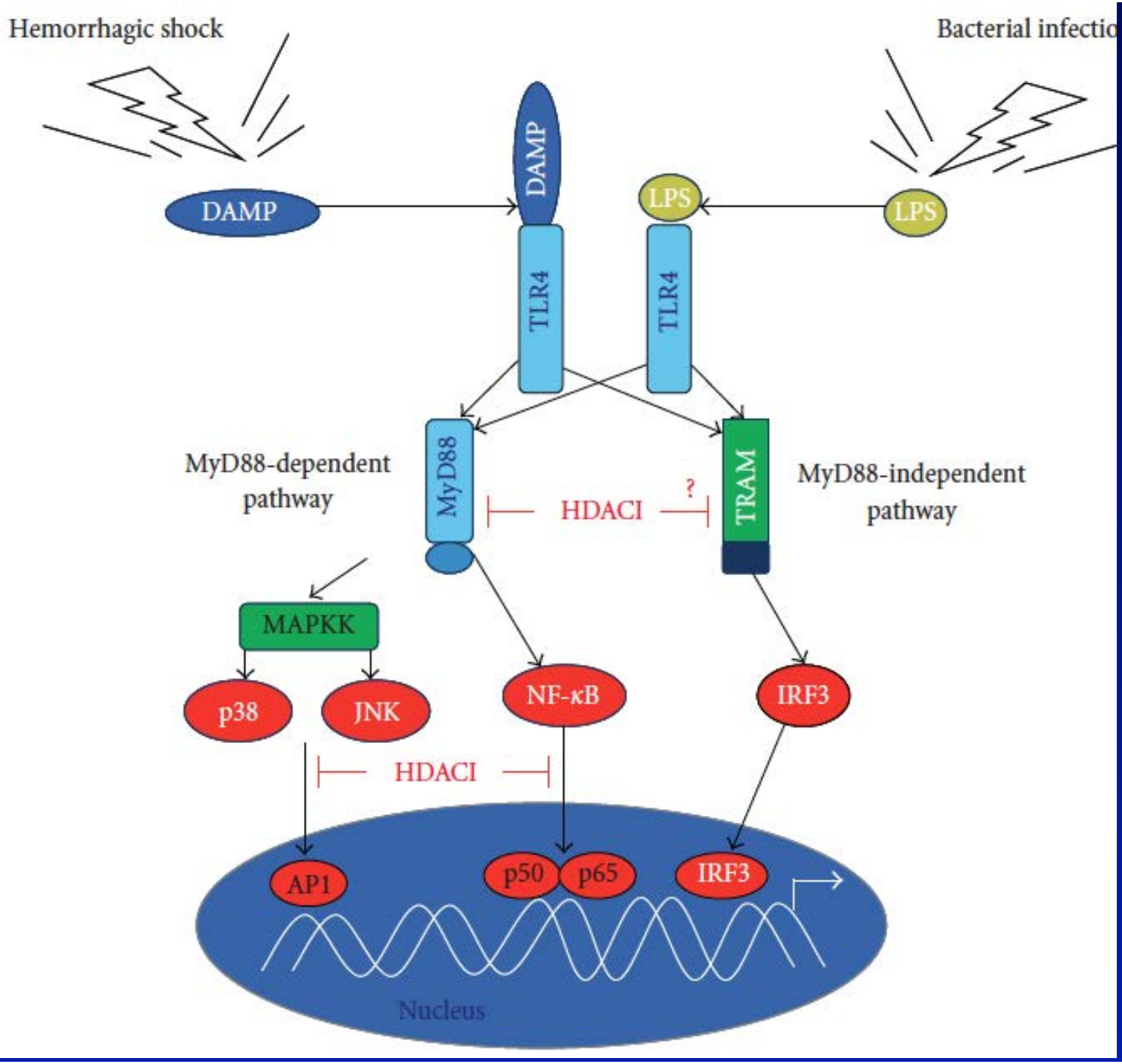
Wei Chong, MD, PhD,[a,b] Yongqing Li, MD, PhD,[a,] Baoling Liu, MD,[a] Ting Zhao, MD,[a] Eugene Y. Fukudome, MD,[a] Zhengcai Liu, MD, PhD,[a,c] William M. Smith,[a] George C. Velmahos, MD, PhD,[a] Marc A. deMoya, MD,[a] and Hasan B. Alam, MD[a]*

[a] *Department of Surgery, Division of Trauma, Emergency Surgery and Surgical Critical Care, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts*

[b] *Emergency Department, the First Hospital, China Medical University, Shenyang, China*

[c] *Department of Hepatobiliary Surgery, Xijing Hospital, the Fourth Military Medical University, Xi'an, China*

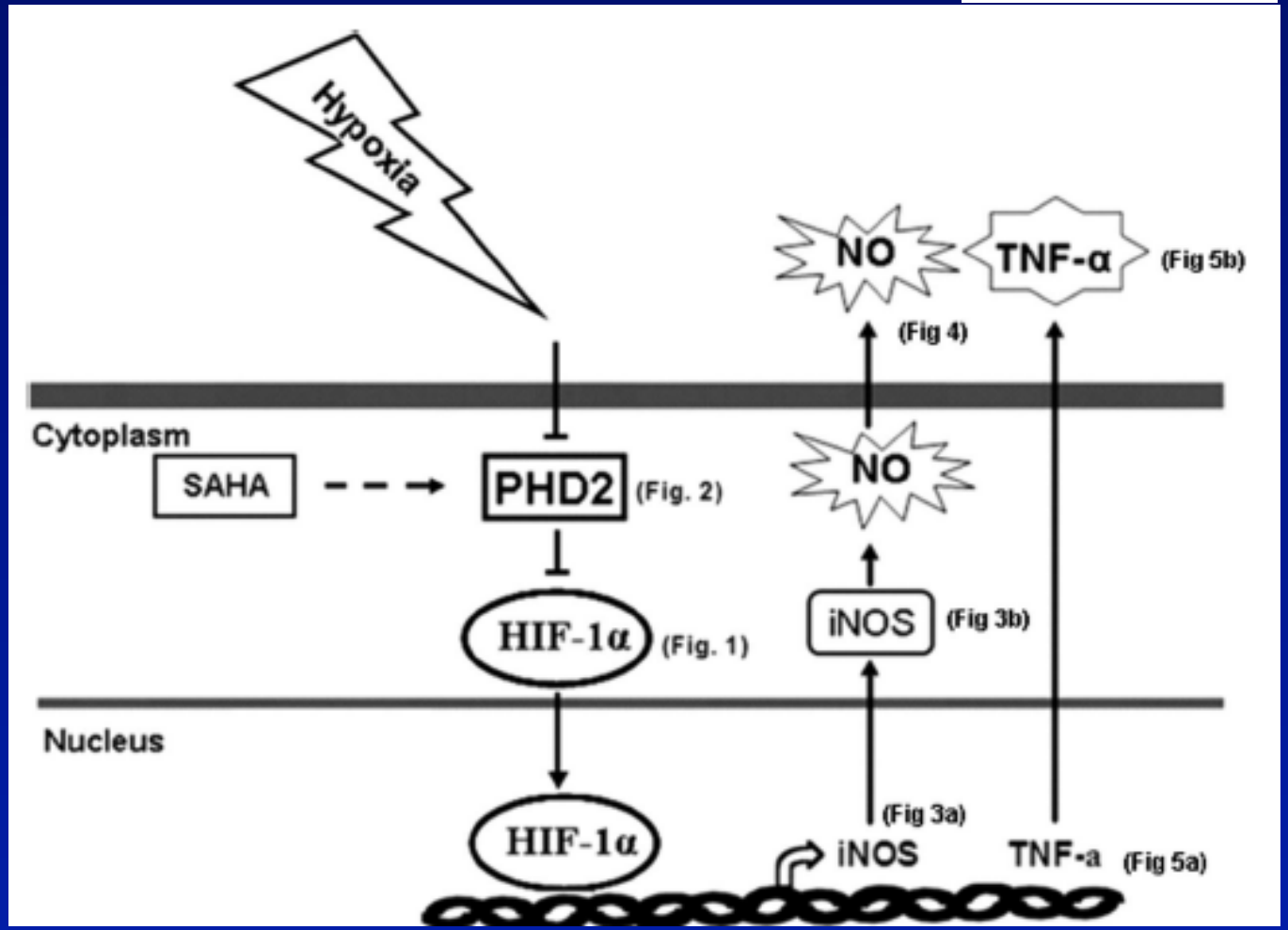
J Surg Res 2012


Hemorrhagic shock
Bacterial infectio
DAMP
DAMP
LPS
LPS
TLR4
TLR4
MyD88-dependent pathway
MyD88
HDACI
?
TRAM
MyD88-independent pathway
MAPKK
p38
JNK
NF-κB
IRF3
HDACI
AP1
p50
p65
IRF3
Nucleus

Anti-inflammatory properties of histone deacetylase inhibitors: A mechanistic study

Wei Chong, MD, PhD, Yongqing Li, MD, PhD, Baoling Liu, MD, Zhengcai Liu, MD, PhD, Ting Zhao, MD, Diane R. Wonsey, PhD, Changmin Chen, PhD, George C. Velmahos, MD, PhD, Marc A. deMoya, MD, David R. King, MD, Andrew L. Kung, MD, PhD. *and* Hasan B. Alam, MD, *Boston, Massachusetts*

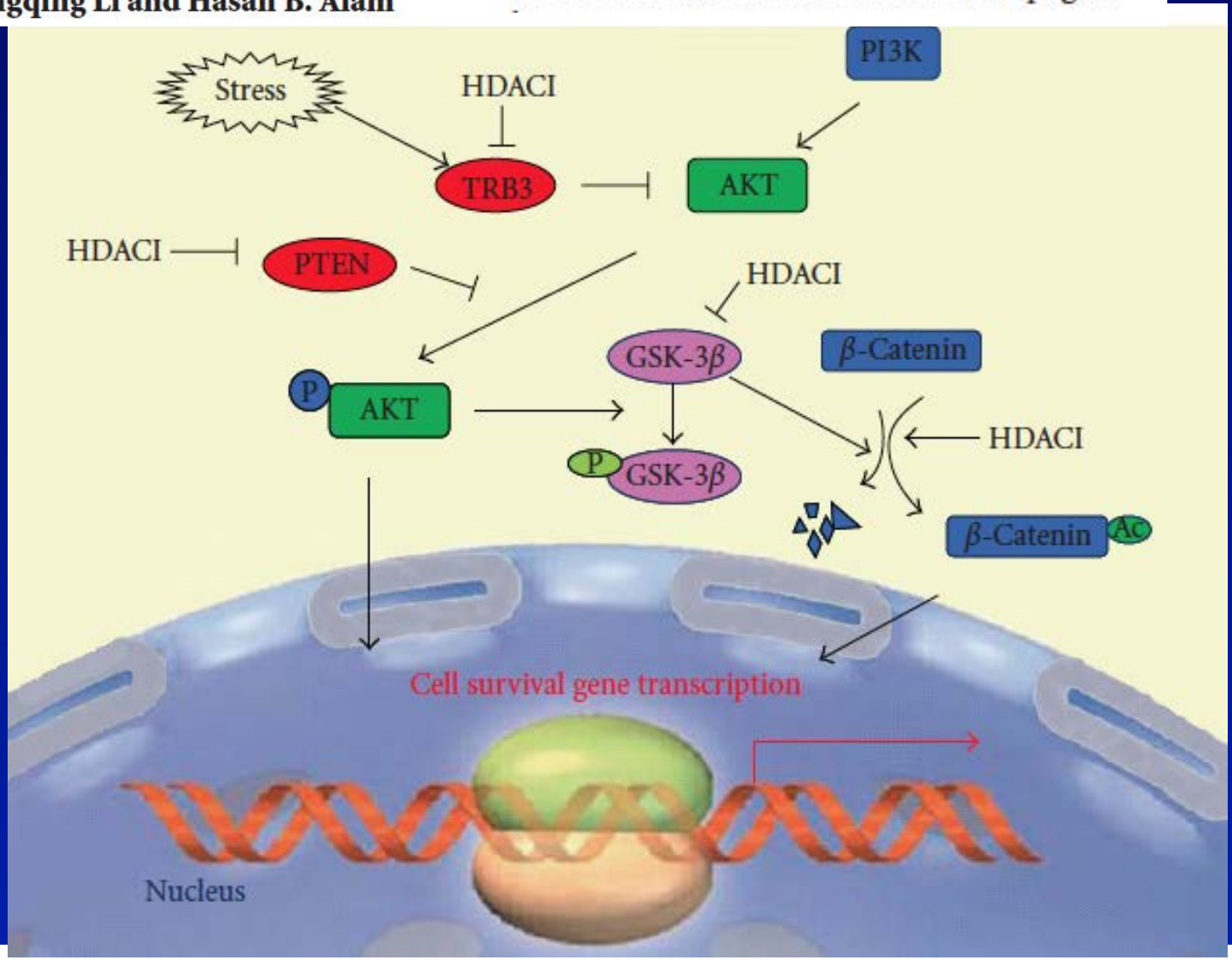
J Trauma
Volume 72, Number 2

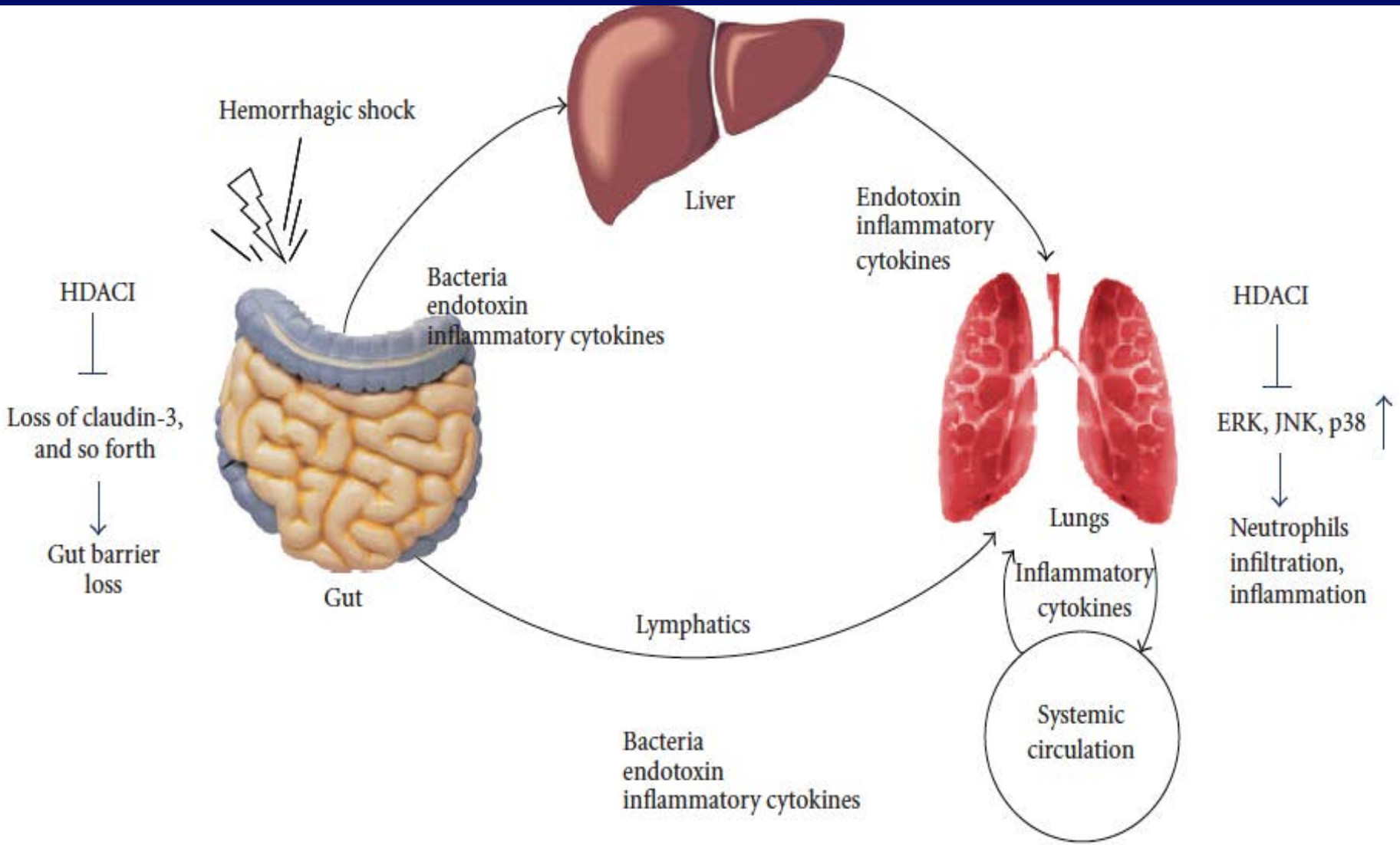


Modulation of Acetylation: Creating a Pro-survival and Anti-Inflammatory Phenotype in Lethal Hemorrhagic and Septic Shock

Yongqing Li and Hasan B. Alam

Journal of Biomedicine and Biotechnology
Volume 2011, Article ID 523481, 15 pages




Hemorrhagic shock
Liver
Endotoxin
inflammatory
cytokines
HDACI
Bacteria
endotoxin
inflammatory cytokines
HDACI
Loss of claudin-3,
and so forth
ERK, JNK, p38
Gut barrier
loss
Neutrophils
infiltration,
inflammation
Gut
Lungs
Inflammatory
cytokines
Lymphatics
Systemic
circulation
Bacteria
endotoxin
inflammatory cytokines

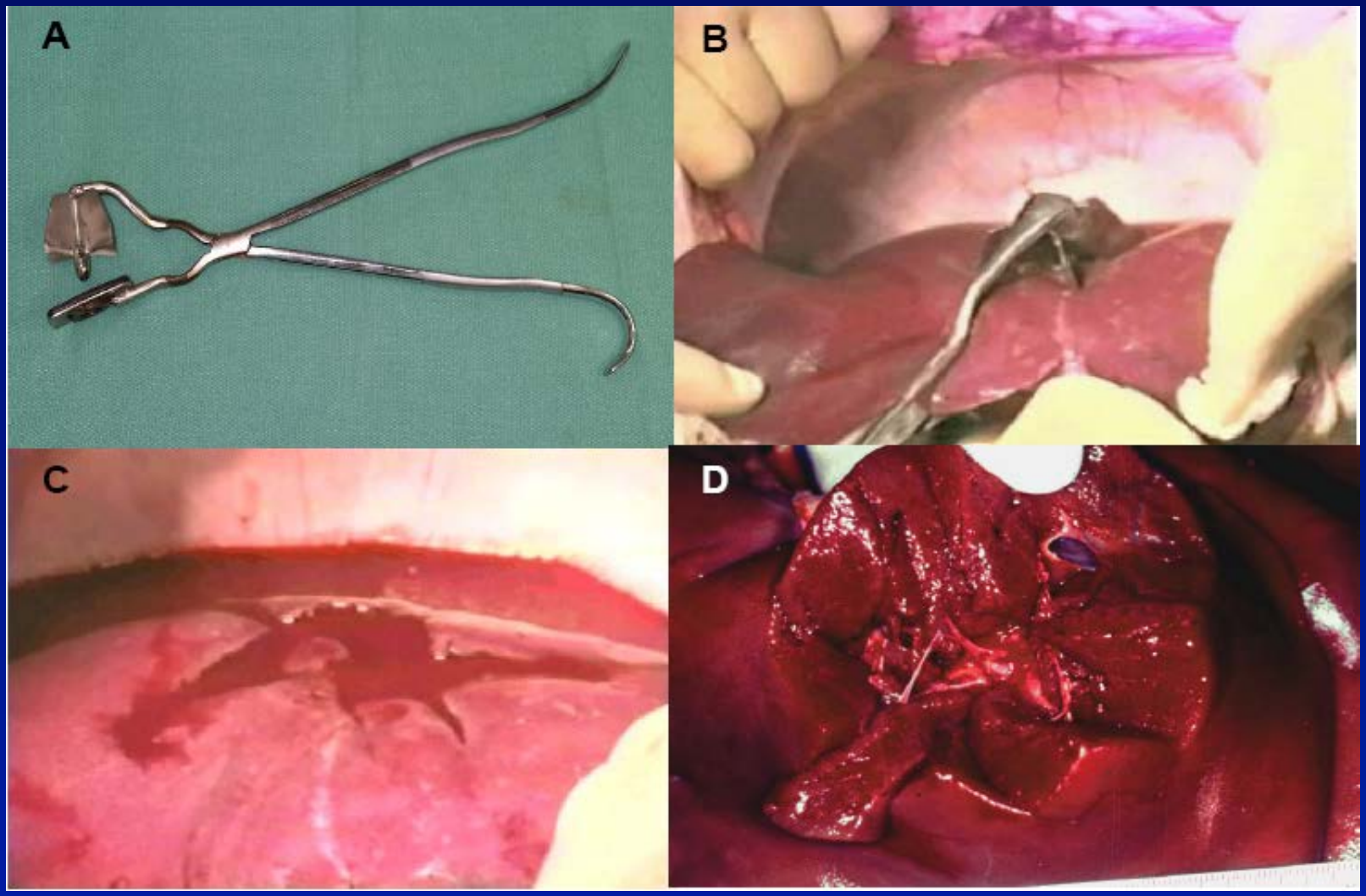
Surviving blood loss without blood transfusion in a swine poly-trauma model

Hasan B. Alam, MD,* Fahad Shuja, MD,* Muhammad U. Butt, MD, Michael Duggan, DVM, Yongqing Li, MD, PhD, Nikolaos Zacharias, MD, Eugene Y. Fukudome, MD, Baoling Liu, MD, Marc deMoya, MD, *and* **George C. Velmahos, MD,** *Boston, Massachusetts*

Surgery 2009

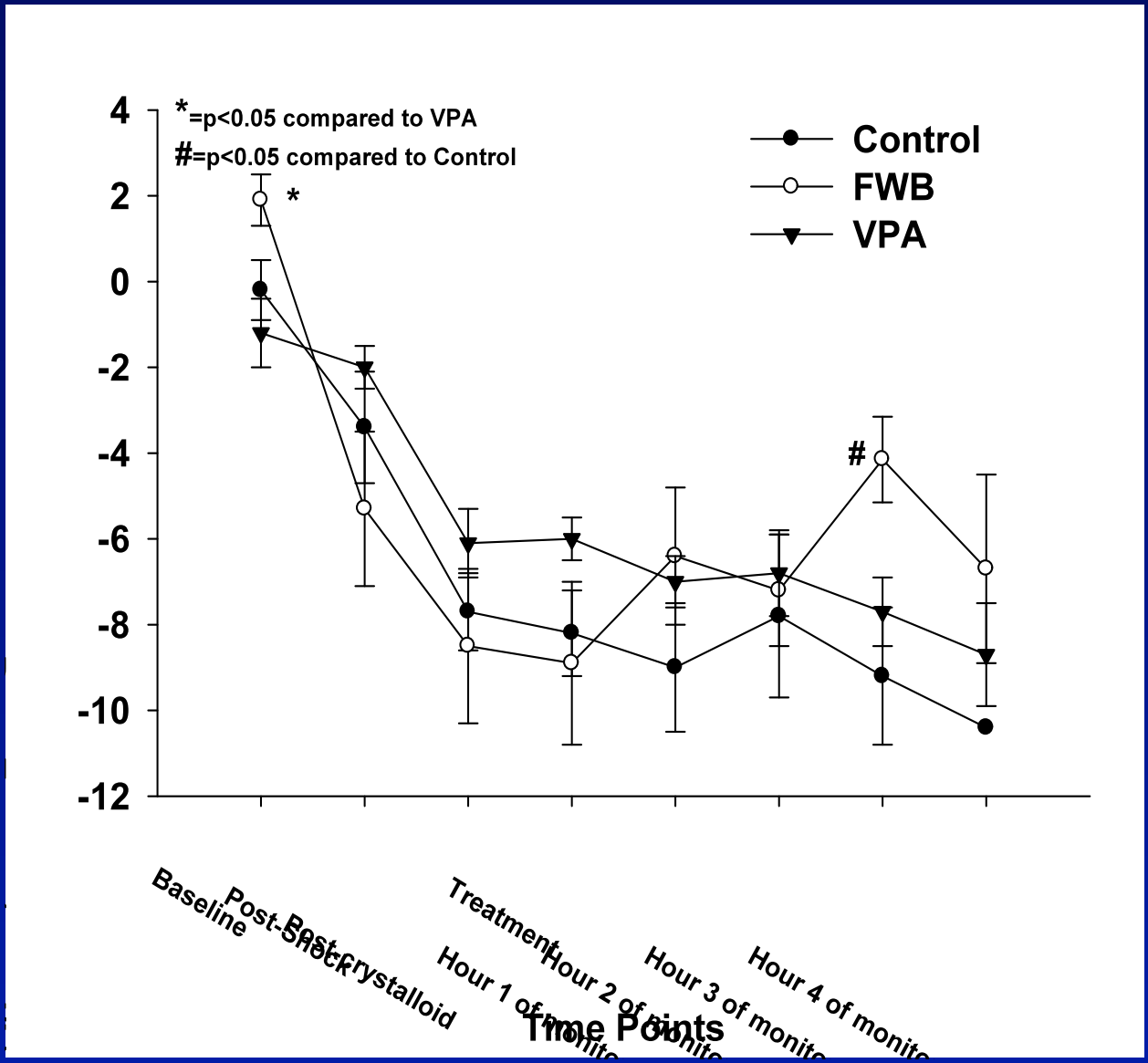
3-D CT image of femur fracture

Image provided by: Jill Sondeen, PhD (USAISR)

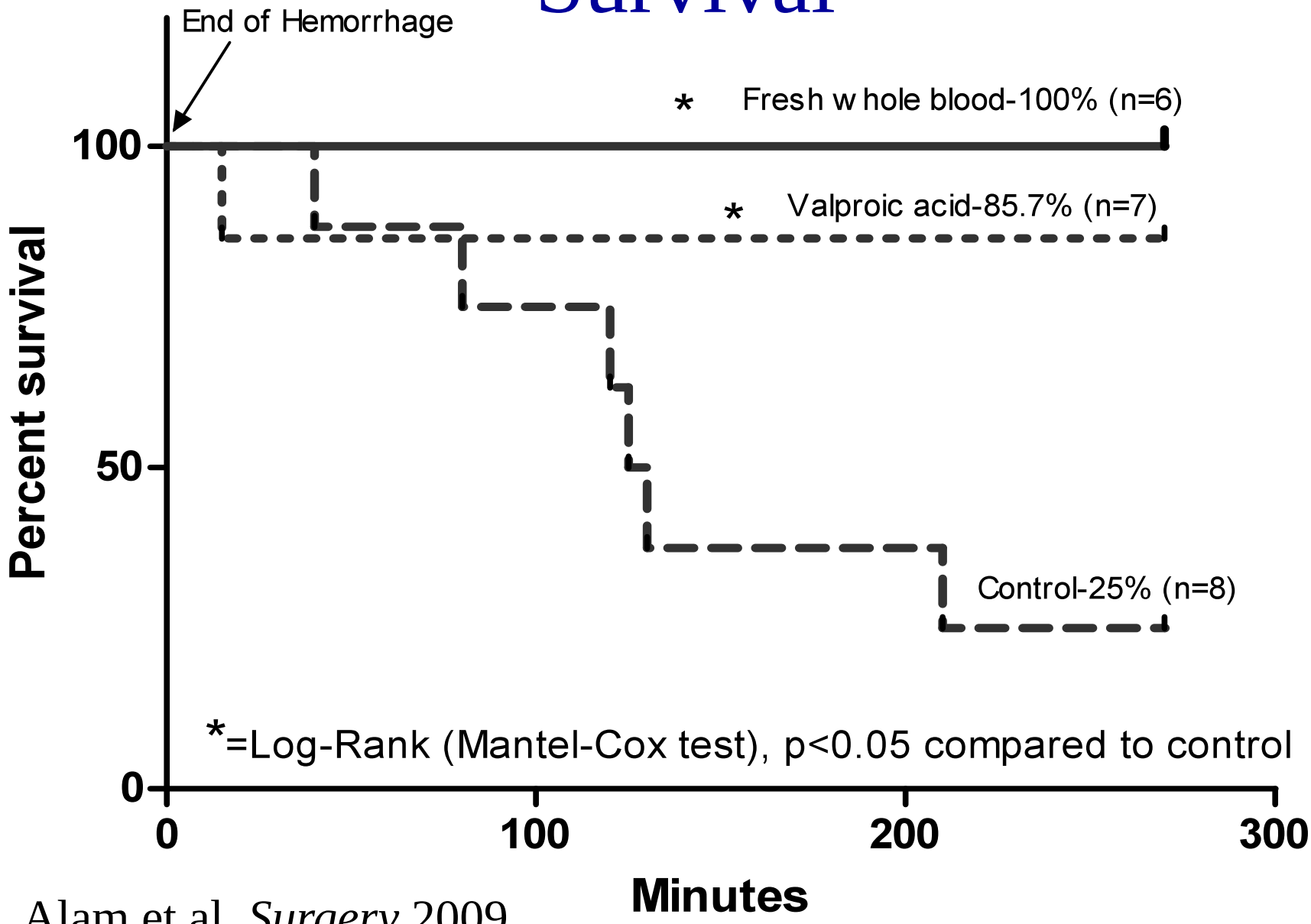


Holcomb JB, et al. Model developed at the US Army ISR, Fort Sam Houston, TX

Base excess


*=p<0.05 compared to VPA
#=p<0.05 compared to Control
Control
FWB
VPA
4
2
0
-2
-4
-6
-8
-10
-12
*
#
Baseline
Post-Shock
Post-Crystalloid
Treatment
Hour 2 of
Hour 3 of monito
Hour 4 of monito
Time Points

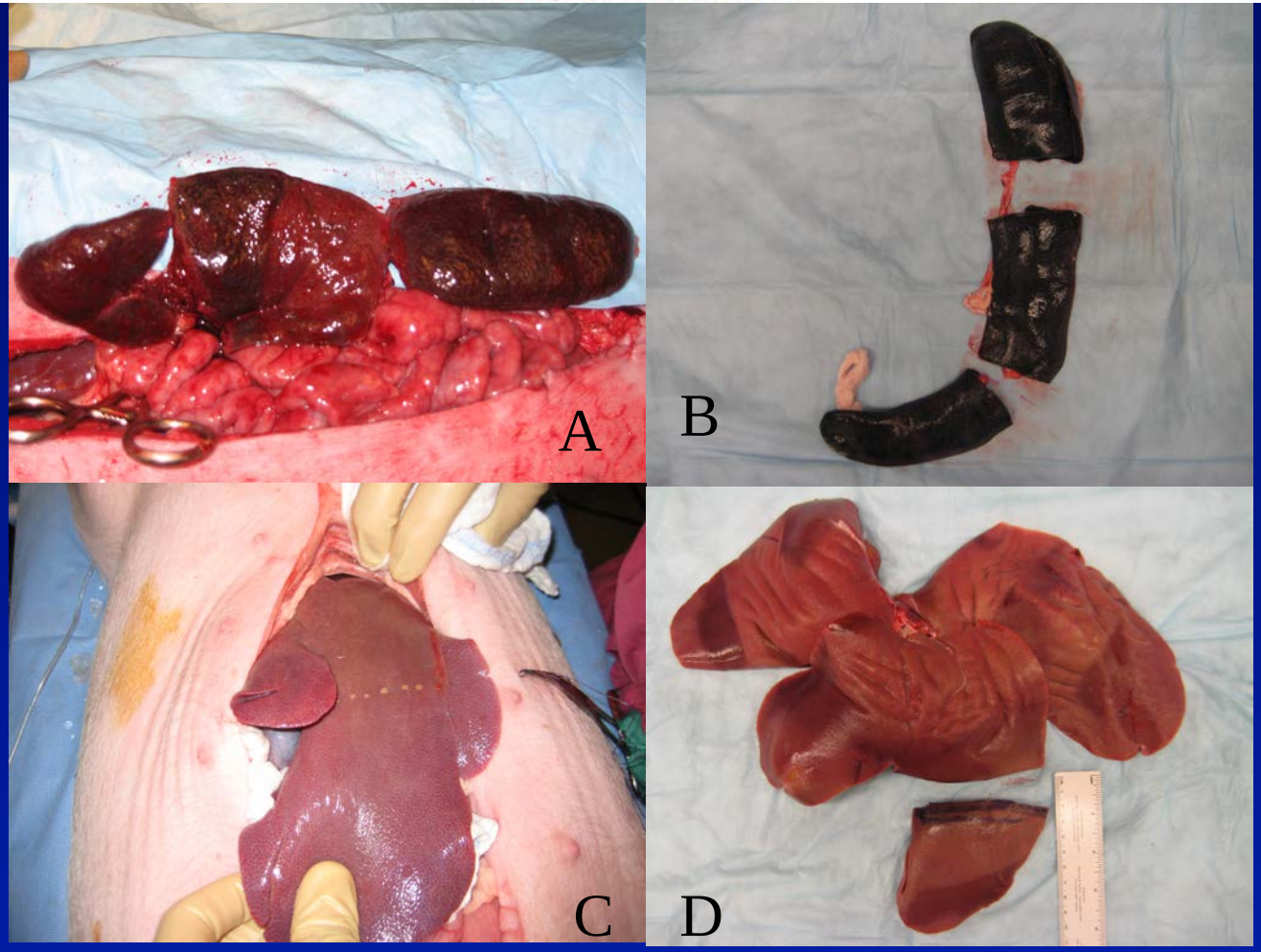
Survival



Alam et al. *Surgery* 2009

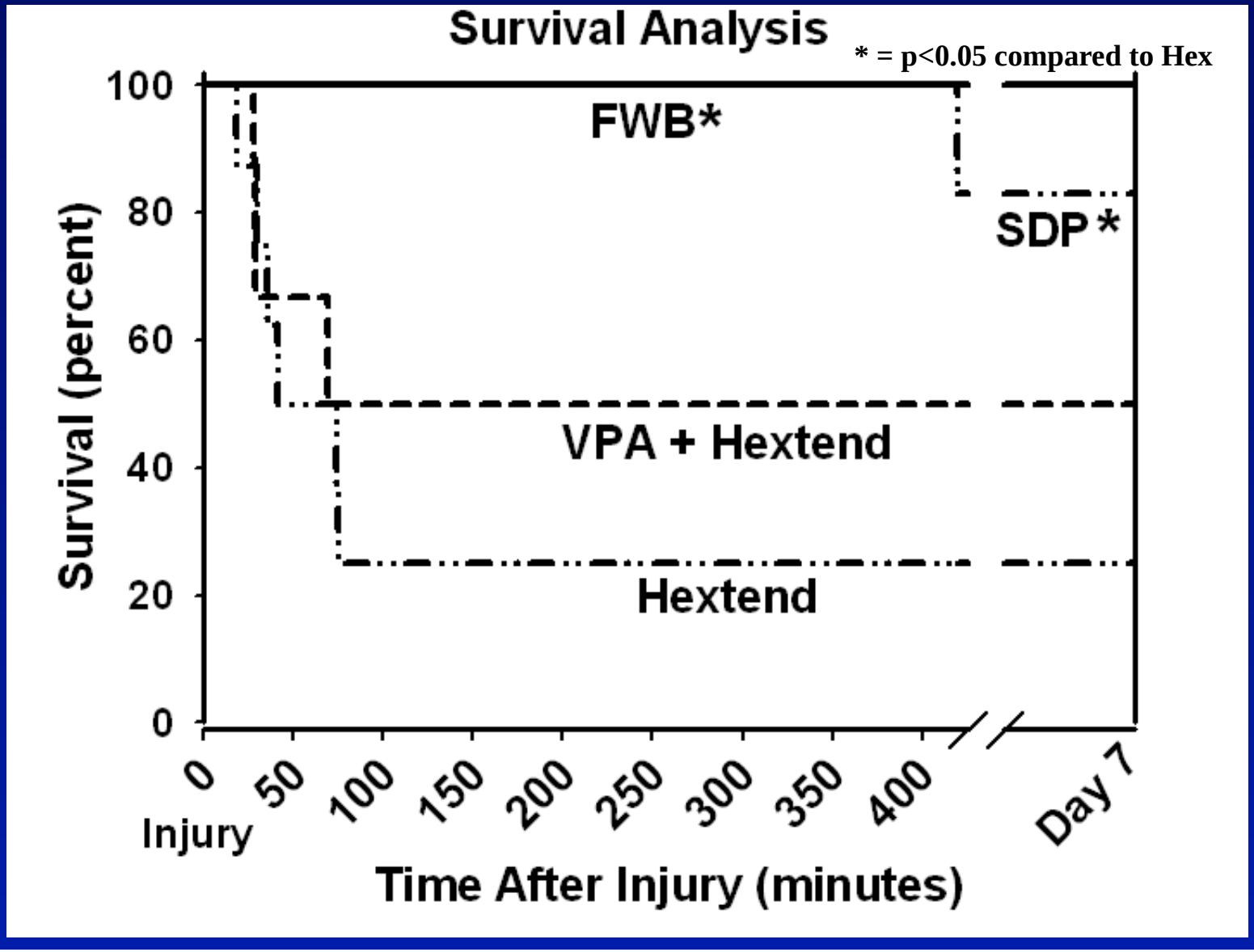
Hemostatic and Pharmacologic Resuscitation: Results of a Long-Term Survival Study in a Swine PolyTrauma Model

Hasan B. Alam, MD, Kristopher B. Hamwi, MD, Michael Duggan, DVM, Karim Fikry, MD, Jennifer Lu, BS, Eugene Y. Fukudome, MD, Wei Chong, MD, PhD, Athanasios Bramos, MD, Kyuseok Kim, MD, PhD, and George Velmahos, MD, PhD

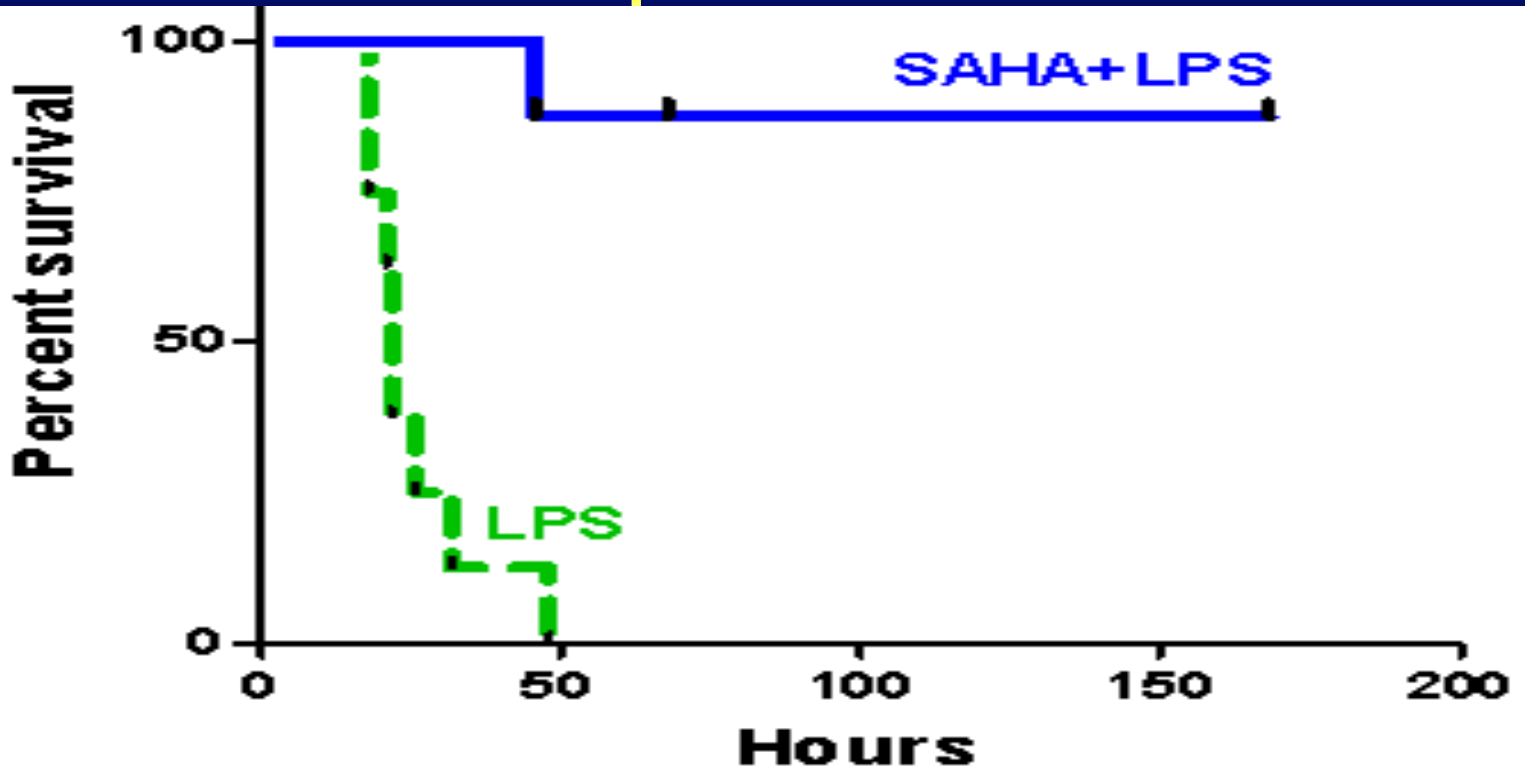


The Journal of **TRAUMA**® *Injury, Infection, and Critical Care* • Volume 70, Number 3, March 2011

Survival


Survival Analysis
* = p<0.05 compared to Hex
FWB*
SDP*
VPA + Hextend
Hextend
Survival (percent)
100
80
60
40
20
0
0
50
100
150
200
250
300
350
400
Day 7
Injury
Time After Injury (minutes)

Septic Shock



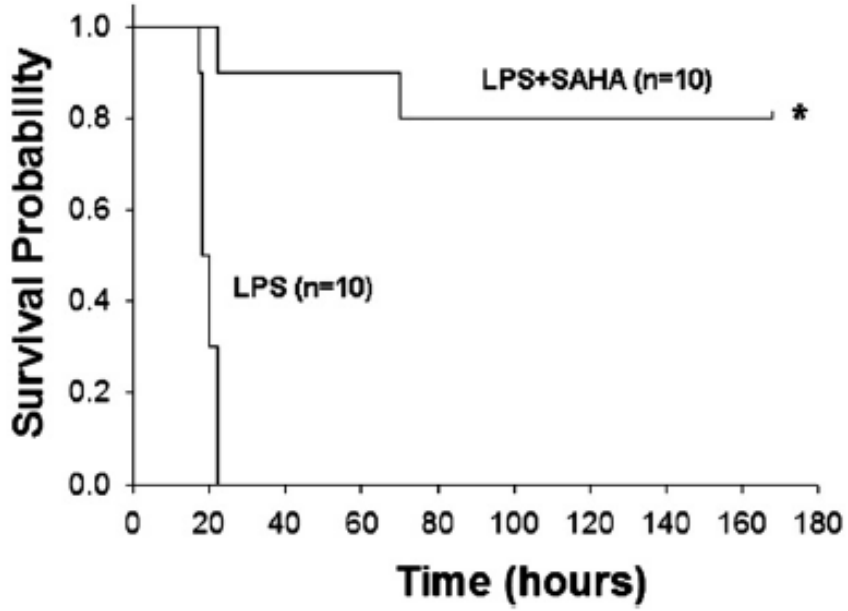
PROTECTIVE EFFECT OF SUBEROYLANILIDE HYDROXAMIC ACID AGAINST LPS-INDUCED SEPTIC SHOCK IN RODENTS

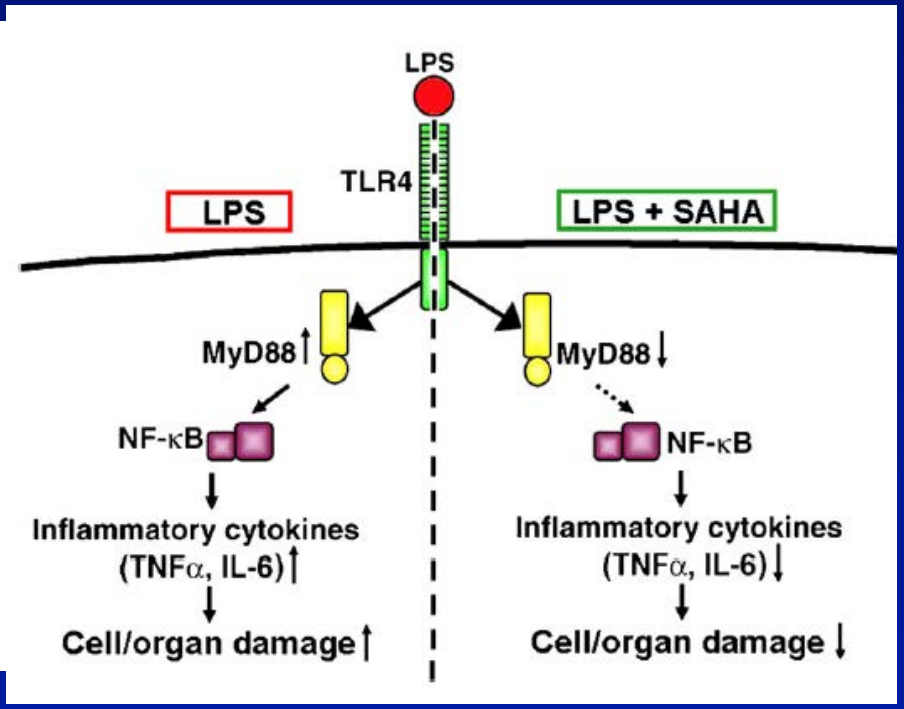
Yongqing Li,* Baoling Liu,* Hang Zhao,† Eugene Y. Fukudome,* Xiaobo Zhang,‡ Tareq Kheirbek,* Robert Finkelstein,* George Velmahos,* Marc deMoya,* Charles A. Hales,† and Hasan B. Alam*

Shock 2009 March [E Pub ahead of print]

Surviving lethal septic shock without fluid resuscitation in a rodent model

Yongqing Li, MD, PhD,[a] Baoling Liu, MD,[a] Eugene Y. Fukudome, MD,[a] Ashley R. Kochanek, BS,[a] Robert A. Finkelstein, MD, CM,[a,b] Wei Chong, MD, PhD,[a] Guang Jin, MD, PhD,[a] Jennifer Lu, BS,[a] Marc A. deMoya, MD,[a] George C. Velmahos, MD, PhD,[a] *and* Hasan B. Alam, MD, FACS,[a] *Boston, MA*





Surgery 2010;148:246-54.

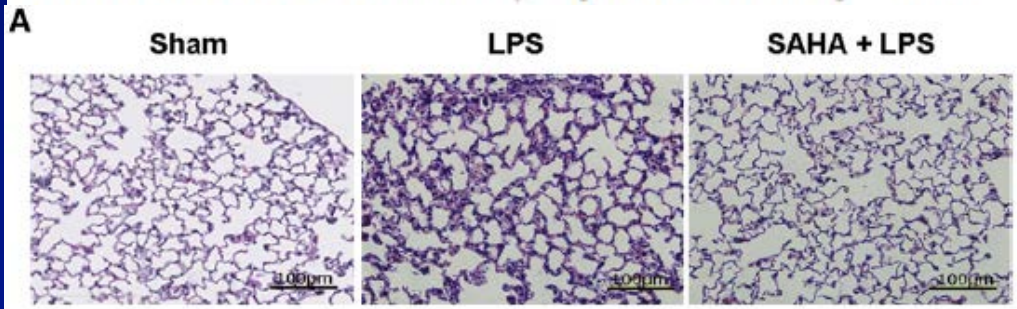
Post-treatment equally effective

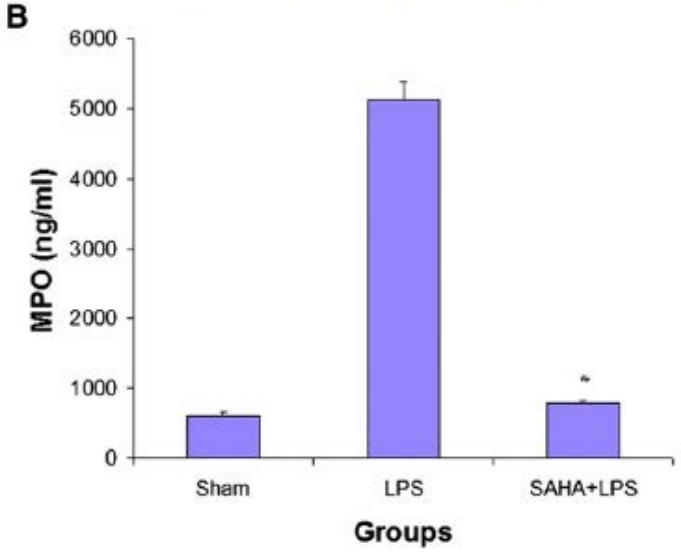
Creating a "pro-survival" phenotype through epigenetic modulation

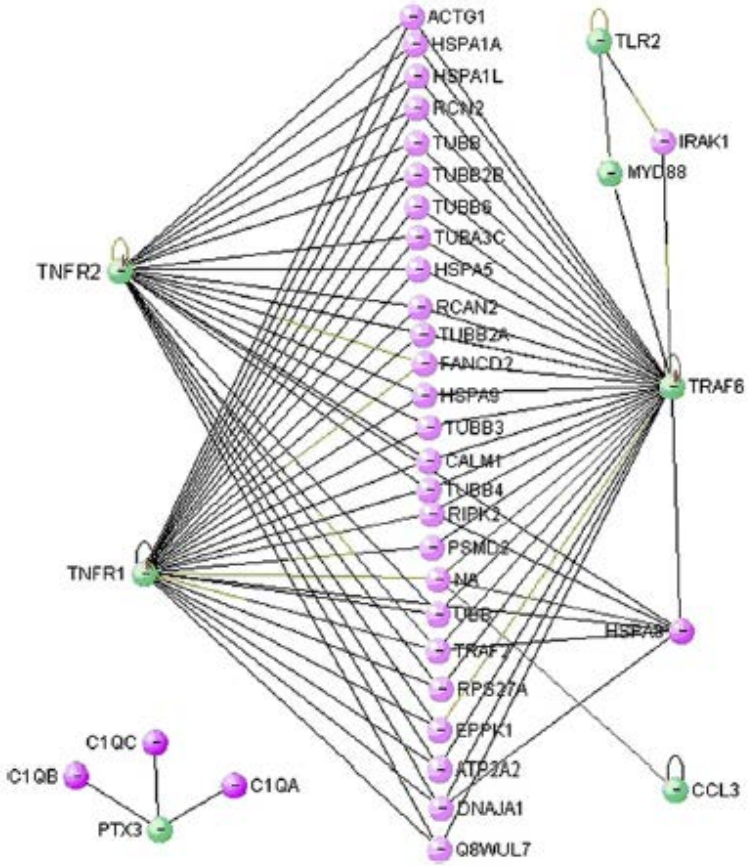
Yongqing Li, MD, PhD,[a] Baoling Liu, MD,[a] Xuesong Gu, PhD,[b] Ashley R. Kochanek, MD,[a] Eugene Y. Fukudome, MD,[a] Zhengcai Liu, MD, PhD,[a,c] Ting Zhao, MD,[a] Wei Chong, MD, PhD,[a,d] Yili Zhao,[a] Dainan Zhang, PhD,[e] Towia A. Libermann, PhD,[b] *and* Hasan B. Alam, MD, FACS,[a]

Boston, MA, and Xi'an, Shenyang, and Xinxiang, China

Surgery 2012;152:455-64.







CLP model

Novel pharmacologic treatment attenuates septic shock and improves long-term survival

Surgery
August 2013

Ting Zhao, MD,[a] Yongqing Li, MD, PhD,[a] Baoling Liu, MD,[a,b] Zhengcai Liu, MD, PhD,[a,c] Wei Chong, MD, PhD,[a,d] Xiuzhen Duan, MD, PhD,[e] Danielle K. Deperalta, MD,[a] George C. Velmahos, MD, PhD,[a] *and* **Hasan B. Alam, MD,[a,b]** *Boston, MA, Ann Arbor, MI, Xi'an and Shenyang, China, and Maywood, IL*

Trauma patients

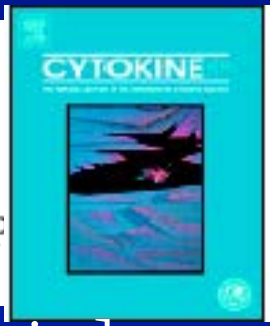
Acetylation: a novel method for modulation of the immune response following trauma/hemorrhage and inflammatory second hit in animals and humans

Elizabeth A. Sailhamer, MD,[a] Yongqing Li, MD, PhD,[a] Eleanor J. Smith,[a] Fahad Shuja, MD,[a] Christian Shults, MD,[a,c] Baoling Liu, MD,[a] Chad Soupir, MD,[b] Marc deMoya, MD,[a] George Velmahos, MD,[a] *and* Hasan B. Alam, MD,[a] *Boston, Mass and Washington, DC*

Surgery 2008

Hypoxic "second hit" in leukocytes from trauma patients: Modulation of the immune response by histone deacetylase inhibition

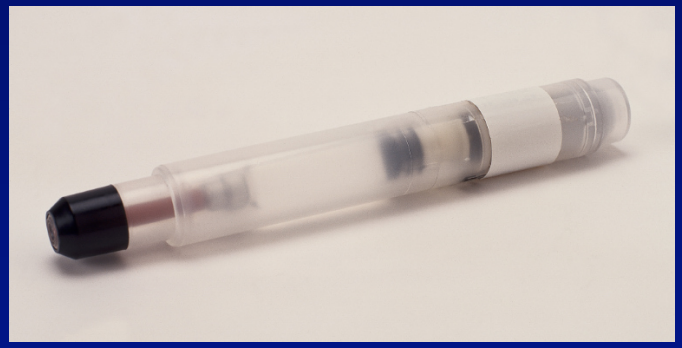
Elizabeth A. Sailhamer [a], Yongqing Li [a], Eleanor J. Smith [a], Baoling Liu [a], Fahad Shuja [a], Chad F
Marc A. DeMoya [a], George C. Velmahos [a], Hasan B. Alam [a,*]



Cytokine 2010 [Epub ahead of print]

Histone deacetylase Inhibitors

- In models of lethal shock HDACI treatment:
  - Improves survival
  - Prevents apoptosis
  - Reduces organ dysfunction
  - Activates survival pathways
  - Modulates inflammatory response



- Human in-vitro data
- “Resuscitation in a syringe”
- ~$10 Million new funding- NIH, DoD

FDA approval for clinical trial 2012

A Study to Evaluate the Safety and Tolerability of Valproic Acid in Healthy Volunteers or Trauma Patients

This study is currently recruiting participants.

Verified September 2013 by University of Michigan

Sponsor:
Dr. **Hasan Alam**

Information provided by (Responsible Party):
Dr. Hasan Alam, University of Michigan

ClinicalTrials.gov Identifier:
NCT01951560

First received: September 23, 2013
Last updated: NA
Last verified: September 2013
History: No changes posted

Purpose

The purpose of the first part of this study is to determine the safety and tolerability of ascending doses of valproic acid (also known as Depacon) administered as intravenous

“Damage Control” Resuscitation

- Permissive hypotension
- Limited crystalloids
- Early blood products
- Prevention of coagulopathy

DEPARTMENT OF THE ARMY
HEADQUARTERS, UNITED STATES ARMY MEDICAL COMMAND
2050 WORTH ROAD
FORT SAM HOUSTON, TX 78234-6000

REPLY TO
ATTENTION OF

MCCG

03 JAN 2007

MEMORANDUM FOR SEE DISTRIBUTION

SUBJECT: Optimal Resuscitation of Severely Injured Soldiers

1. Combat resuscitation data analyzed by the US Army Institute of Surgical Research (USAISR) demonstrate that casualties who receive more than 10 units of packed red blood cells (PRBCs) in a 24 hour period (massive transfusion) have a profound survival benefit when the plasma (FFP) to PRBC transfusion ratio is 1:1. Casualties who receive less FFP (1 unit FFP to 4 units PRBCs, or less) have an overall mortality of 65%, while those who receive a 1:1 ratio have an overall mortality of 20% ($p < 0.001$).

2. Severely injured casualties should have the 1:1 ratio initiated as early after injury as possible. Transfusions must be accomplished according to guidelines established by the CENTCOM Blood Program Manager. The current approved CENTCOM Clinical Practice Guideline for Damage Control Resuscitation and Transfusion is posted on the Joint Patient Tracking Application (JPTA) website: https://jpta.fhp.osd.mil/PatientInformation/secured/loginIrmc.aspx?ReturnUrl=%2fPatientInformation%2fsecured%2fdefault.aspx.

3. No new equipment is required to implement this change in clinical resuscitation practice. Training is currently incorporated into the Joint Combat Trauma Management Course (US Army Medical Department Center & School (AMEDDC&S)) and posted on the AMEDDC&S website.

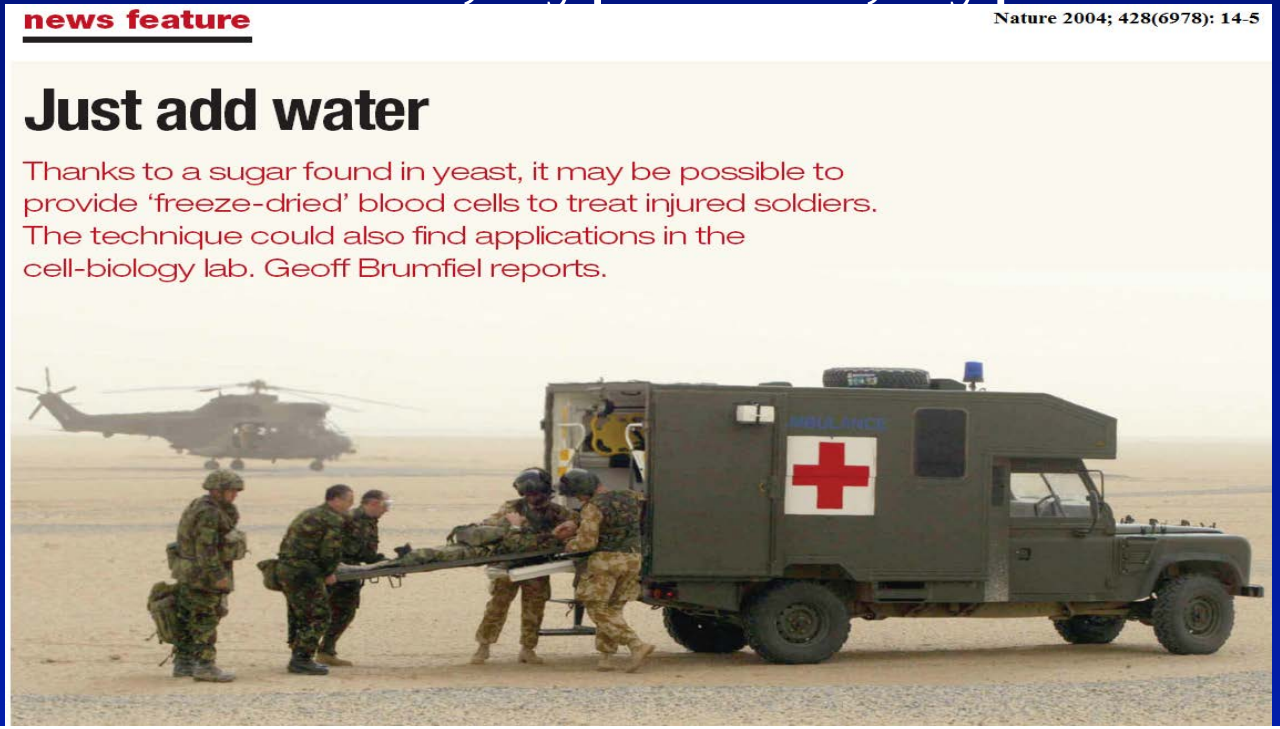
4. POC for this memorandum is COL John Holcomb, Trauma Consultant to The Surgeon General and Commander, USAISR, Ft. Sam Houston, TX, at (210) 916-2720, DSN 429-2720, or e-mail john.holcomb@amedd.army.mil.

KEVIN C. KILEY, M.D.
Lieutenant General
The Surgeon General

Plasma and red cells are good but…

New approach

- Freeze dried plasma and platelets
- Combined with hemoglobin based solution, +/- recombinant factors +/- preserved platelets
- Low volume, hypertonic, hyperoncotic



news feature

Nature 2004; 428(6978): 14-5

Just add water

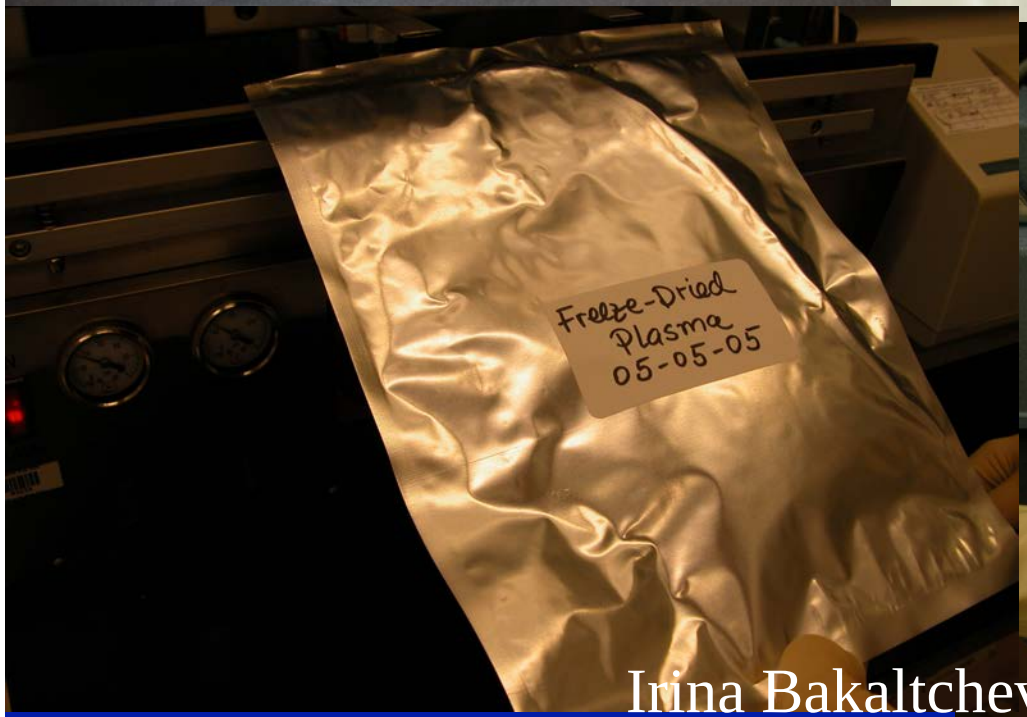
Thanks to a sugar found in yeast, it may be possible to provide 'freeze-dried' blood cells to treat injured soldiers. The technique could also find applications in the cell-biology lab. Geoff Brumfiel reports.

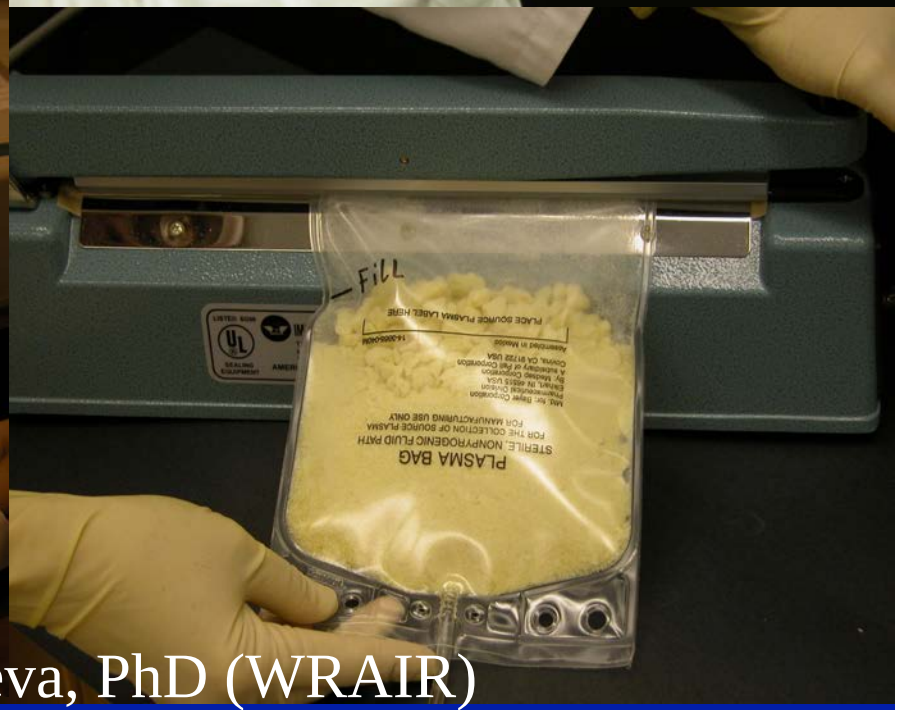
Development and Testing of Freeze-Dried Plasma for the Treatment of Trauma-Associated Coagulopathy

Fahad Shuja, MD, Christian Shults, MD, Michael Duggan, DVM, Malek Tabbara, MD, Muhammad U. Butt, MD, Thomas H. Fischer, PhD, Martin A. Schreiber, MD, Brandon Tieu, MD, John B. Holcomb, MD, Jill L. Sondeen, PhD, Marc deMoya, MD, George C. \ and Hasan B. Alam, MD

J Trauma. 2008;65:000–000.

WTA Squaw Valley 2008





Irina Bakaltcheva, PhD (WRAIR)

Development and Testing of Low-Volume Hyperoncotic, Hyperosmotic Spray-Dried Plasma for the Treatment of Trauma-Associated Coagulopathy

Fahad Shuja, MD, Robert A. Finkelstein, MDCM, Eugene Fukudome, MD, Michael Duggan, DVM, Tareq Kheirbek, MD, Kristopher Hamwi, MD, Thomas H. Fischer, PhD, Karim Fikry, MD, Marc deMoya, MD, George C. Velmahos, MD, and Hasan B. Alam, MD

The Journal of **TRAUMA**® *Injury, Infection, and Critical Care* • Volume 70, Number 3, March 2011

- Spray dried
- 1/3rd volume
- Just as good as FFP
- Easy to reconstitute

WTA Telluride 2010

Freeze Dried Plasma- Phase I/II Clinical Trials 2010-12
Spray Dried Plasma- Phase I Clinical Trial 2012-13

Traumatic Brain Injury

Model development

Contents lists available at ScienceDirect

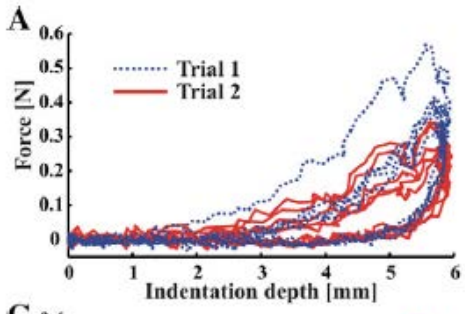
Acta Biomaterialia

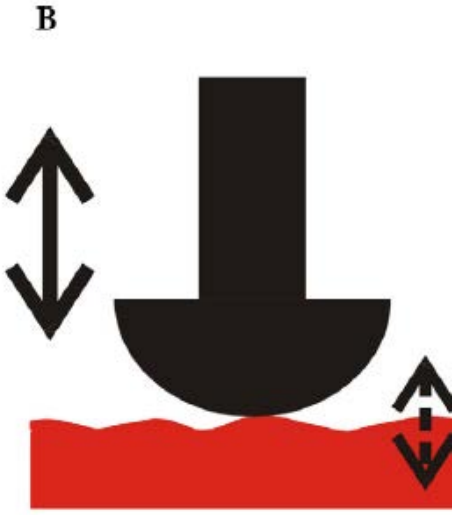
journal homepage: www.elsevier.com/locate/actabiomat

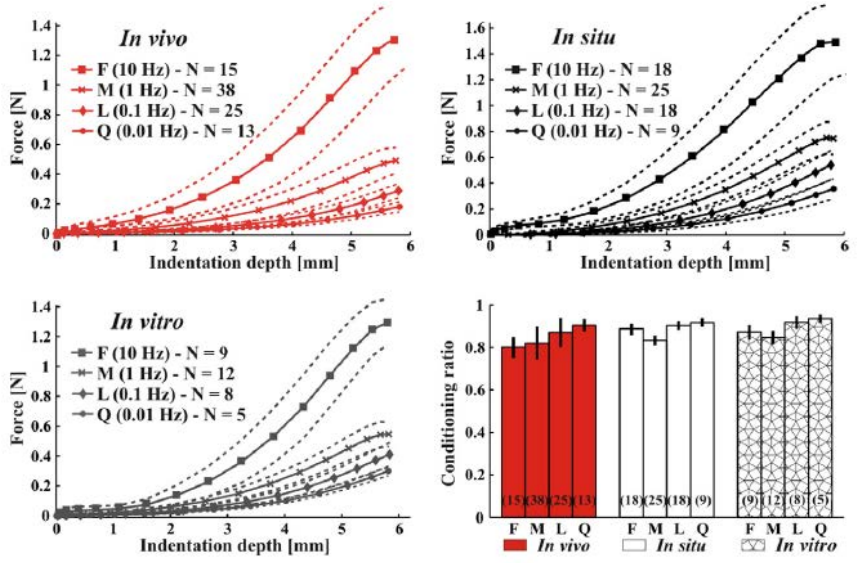
Dynamic mechanical response of brain tissue in indentation in vivo, in situ and in vitro

Thibault P. Prevost[a], Guang Jin[b], Marc A. DeMoya[b], Hasan B. Alam[b], Subra Suresh[a], Simona Socrate[c,*]

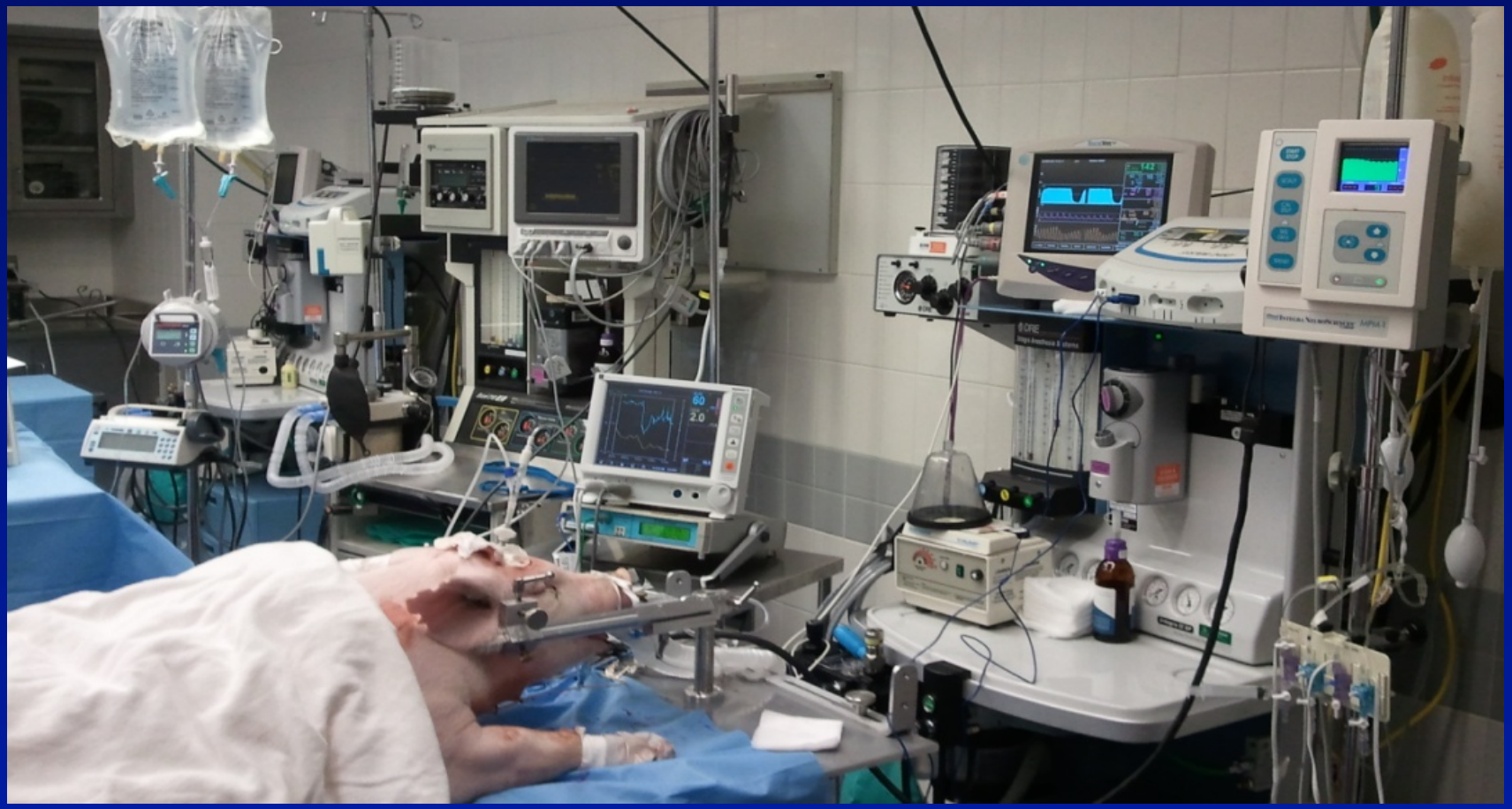
2011



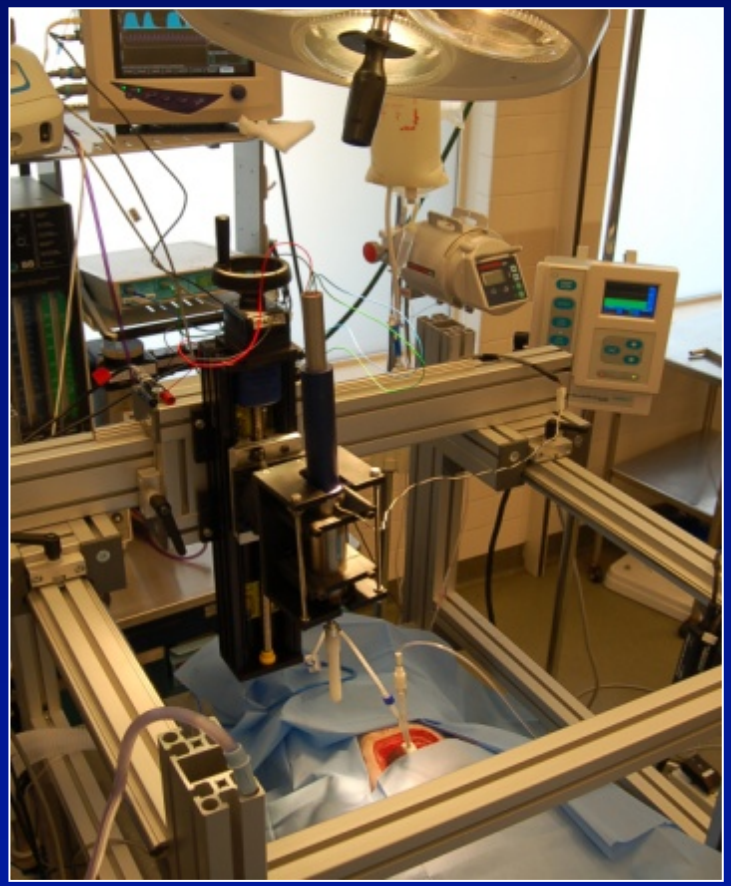




Surgery and physiological monitoring



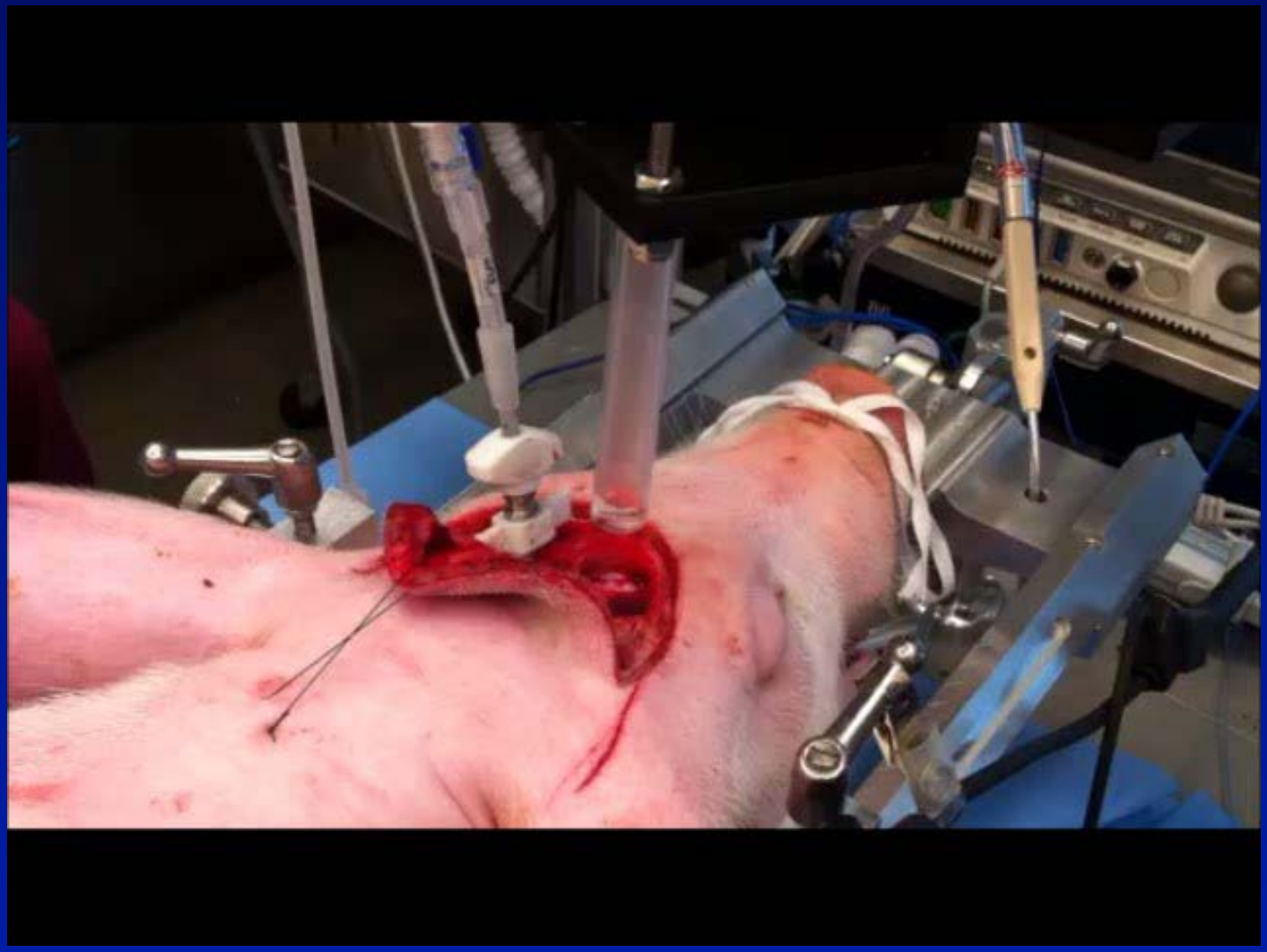
Controlled cortical impact device



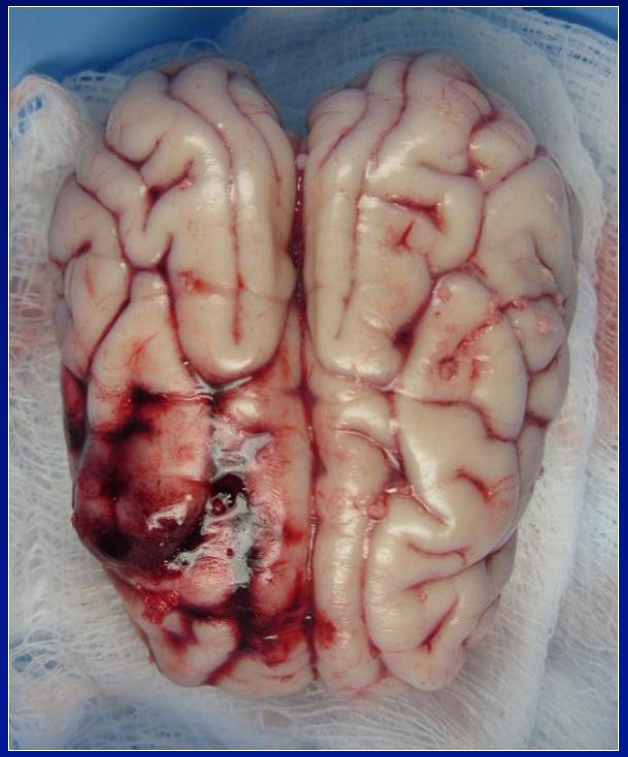
Impactor mounted on an Adjustable frame

Impactor in position before firing

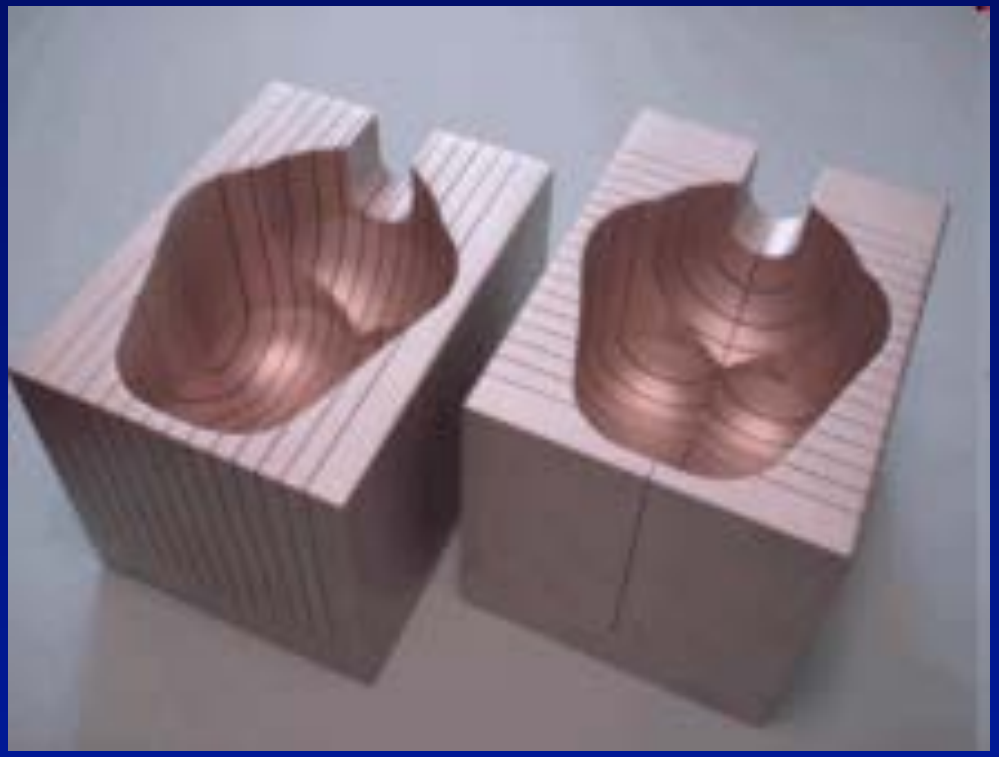
Creating the CCI



Brain coronal sections



Brain post-CCI

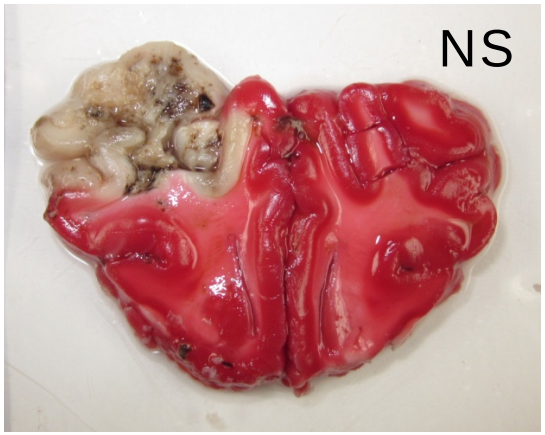


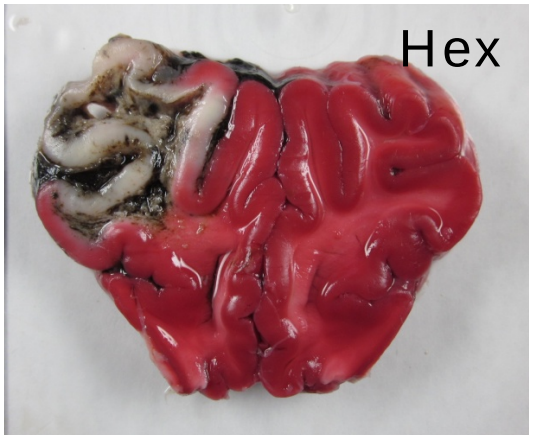
Brain slicer, 5 mm thickness

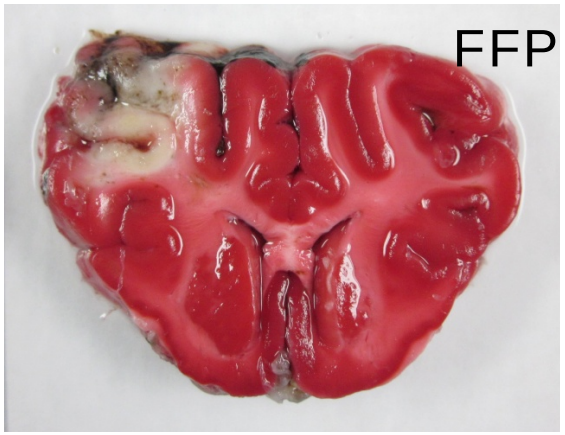
Brain swelling = [(ipsilateral hemisphere's volume/contralateral hemisphere's volume)−1]×100 (*Takano et al. Stroke 28:1255-62*).

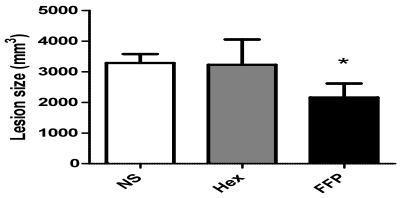
Infarction sizes corrected by the swelling factor (*Jin et al, Translational Stroke Research 2010, 1:65-70*).

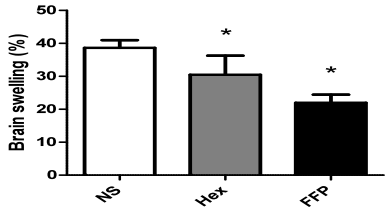
FFP decreases lesion size and brain swelling





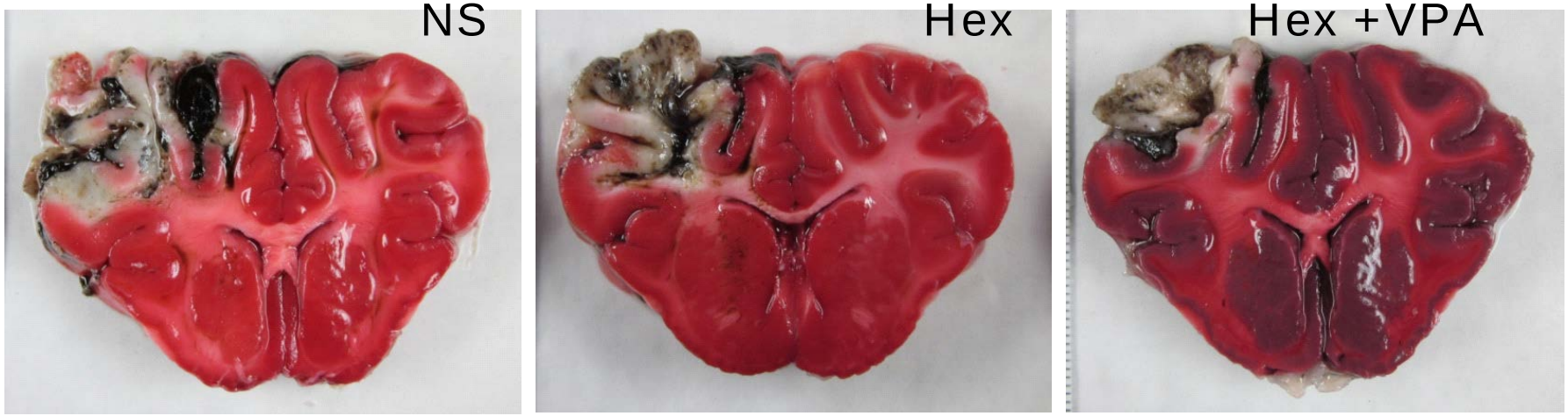


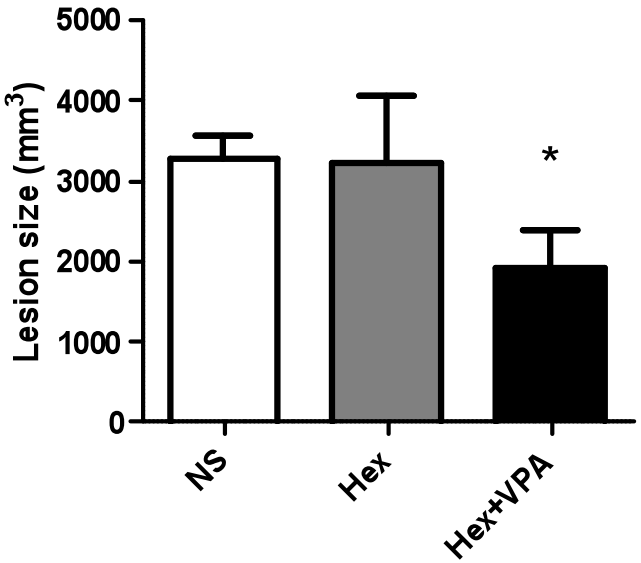


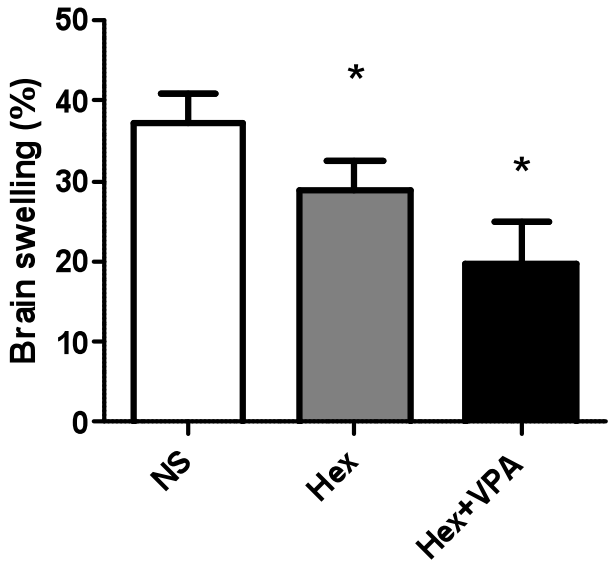


Jin et al. SHOCK 2012

Valproic acid is even more effective

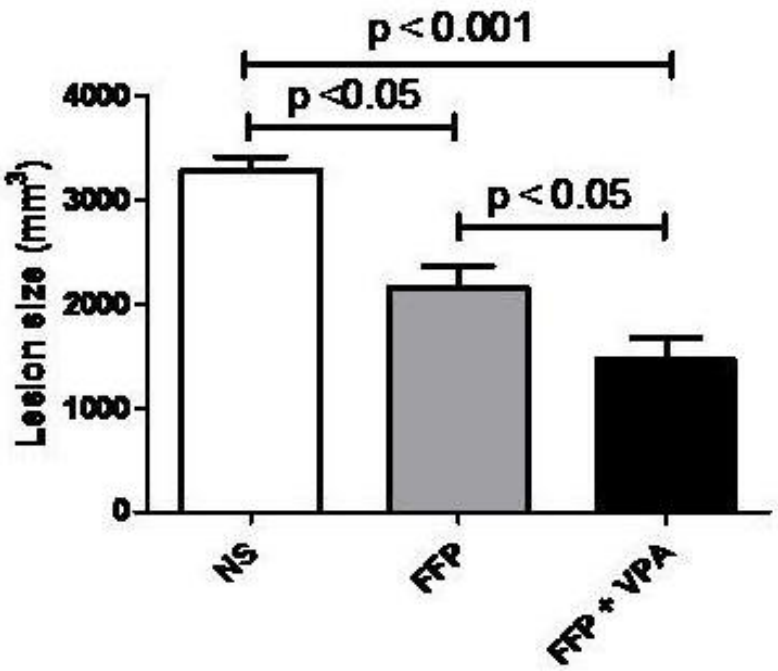


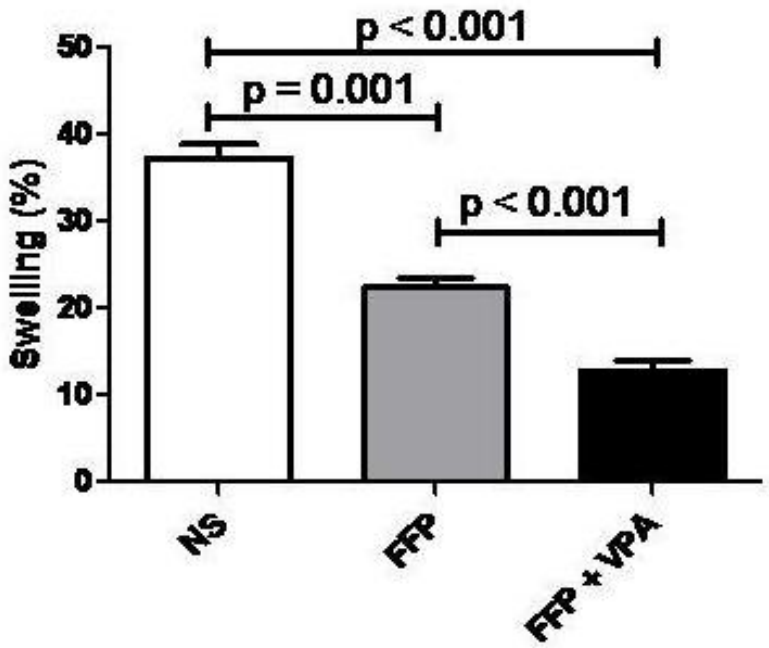




Jin et al. J Trauma 2012. **WTA Vail 2012**

Combination is the best





Imam et al. Surgery 2013

Differential effects of fresh frozen plasma and normal saline on secondary brain damage in a large animal model of polytrauma, hemorrhage and traumatic brain injury

John O. Hwabejire, MD, MPH, Ayesha M. Imam, MD, Guang Jin, MD, PhD, Baoling Liu, MD, Yongqing Li, MD, PhD, Martin Sillesen, MD, Cecilie H. Jepsen, MD, Jennifer Lu, BS, Marc A. deMoya, MD, *and* Hasan B. Alam, MD, *Ann Arbor, Michigan*

WTA Snowmass 2013

WTA 2013 Plenary Paper

Early treatment with lyophilized plasma protects the brain in a large animal model of combined traumatic brain injury and hemorrhagic shock

Ayesha M. Imam, MD, Guang Jin, MD, PhD, Martin Sillesen, MD, Michael Duggan, DVM, Cecilie H. Jepsen, MD, John O. Hwabejire, MD, MPH, Jennifer Lu, BS, Baoling Liu, MD, Marc A. DeMoya, MD, George C. Velmahos, MD, PhD, *and* Hasan B. Alam, MD, *Ann Arbor, Michigan*

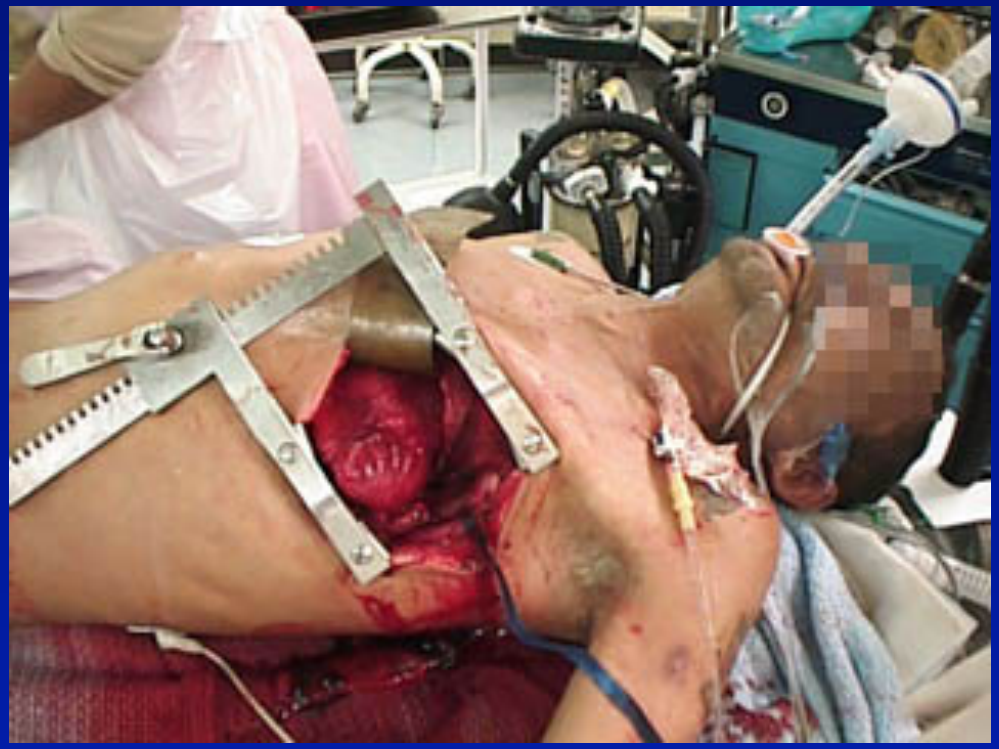
Platelet activation and dysfunction in a large-animal model of traumatic brain injury and hemorrhage

Martin Sillesen, MD, Pär I. Johansson, MD, DMsc, Lars S. Rasmussen, MD, PhD, DMsc, Guang Jin, MD, PhD, Cecilie H. Jepsen, MD, Ayehsa M. Imam, MD, John Hwabejire, MD, MPH, Jennifer Lu, BS, Michael Duggan, DVM, George Velmahos, MD, PhD, Marc deMoya, MD, *and* Hasan B. Alam, MD, *Ann Arbor, Michigan*

(*J Trauma Acute Care Surg.* 2013;74:1252–1259

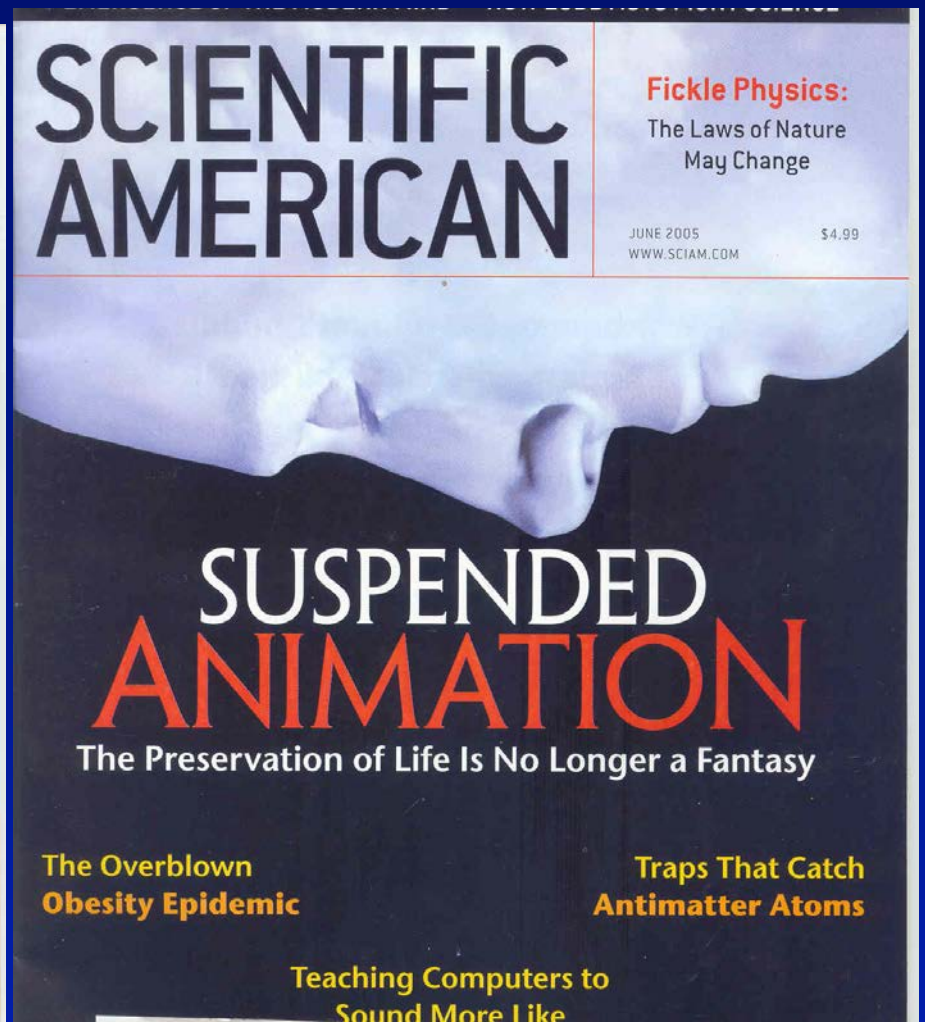
Massive blood loss and no pulse

Emergency Department Thoracotomy




90 1 28

The ultimate resuscitation strategy



The Journal of TRAUMA® Injury, Infection, and Critical Care

Putting Life On Hold—For How Long? Profound Hypothermic Cardiopulmonary Bypass in a Swine Model of Complex Vascular Injuries

Hasan B. Alam, MD, Michael Duggan, DVM, Yongqing Li, MD, PhD, Konstantinos Spaniolas, MD, Baoling Liu, MD, Malek Tabbara, MD, Marc deMoya, MD, Elizabeth A. Sailhan and George C. Velmahos, MD

J Trauma. 2008;64:912–922.

Profound hypothermia is superior to ultraprofound hypothermia in improving survival in a swine model of lethal injuries

Surgery
August 2006

Hasan B. Alam, MD,[a,b] Zheng Chen, MD, PhD,[a] Yongqing Li, MD, PhD,[b] George Velmahos, MD,[b] Marc DeMoya, MD,[b] Christopher E. Keller, DVM, MPH,[c] Kevin Toruno, BS,[a] Tina Mehrani, BS,[a] Peter Rhee, MD, MPH,[a,d] *and* **Konstantinos Spaniolas, MD[b]** *Bethesda, Md, Boston, Mass, and Los Angeles, Calif*

Profound Hypothermia Protects Neurons and Astrocytes, and Preserves Cognitive Functions in a Swine Model of Lethal Hemorrhage[1]

Hasan B. Alam, M.D.,*,§,[1,2] Zhang Chen, M.D., Ph.D.,* Naresh Ahuja, M.D., M.P.H.,*,¶ Huazhen Chen, M.D.,* Richard Conran, M.D.,† Eduardo C. Ayuste, M.D.,* Kevin Toruno, B.S.,* Nanna Ariaban, B.S.,* Peter Rhee, M.D.,*,‡ Amal Nadel, M.S.,* and Elena Koustova, Ph.D.*

Journal of Surgical Research **126,** 172–181 (2005)

Profound Hypothermic Cardiopulmonary Bypass Facilitates Survival Without a High Complication Rate in a Swine Model of Complex Vascular, Splenic, and Colon Injuries

J Am Coll Surg 2007;204:642–653.

Elizabeth A Sailhamer, MD, Zheng Chen, MD, PhD, Naresh Ahuja, MD, George C Velmahos, MD, FACS, Marc de Moya, MD, Peter Rhee, MD, FACS, Christian Shults, MD, Hasan B Alam, MD, FACS

Role of hypothermia in hemorrhagic shock

Journal of Organ Dysfunction, 2008; 4: 151–160

FAHAD SHUJA, JOSÉ PEDRO ALMEIDA and HASAN B. ALAM

Cognitive function testing

Alam et al, Surgery 132:278-288, 2002

- Operant conditioning
- Recognize and open color coded box
- Number of sessions, time to finish task, performance score

Emergency Preservation and Resuscitation

- Rate of induction – Fast (2°C/minute)
  Alam et al. J Trauma 2004
- Optimal Depth – Profound (10°C)
  Alam et al. Surgery 2006
- Rate of re-warming – (0.5°C/minute)
  Alam et al. J Trauma 2006
- Duration – short (60 minutes)
  Alam et al. J Trauma 2008
- Poly-trauma – feasible without complications
  Sailhamer et al. JACS 2007

Profound Hypothermia Decreases Cardiac Apoptosis Through Akt Survival Pathway

Fahad Shuja, MD, Malek Tabbara, MD, Yongqing Li, MD, PhD, Baoling Liu, MD, Muhammad Umar Butt, MD, George C Velmahos, MD, FACS, Marc deMoya, MD, FACS, Hasan B Alam, MD, FACS

J Am Coll Surg 2009;209:89–99.

Alterations in Gene Expression After Induction of Profound Hypothermia for the Treatment of Lethal Hemorrhage

Hasan B. Alam, MD, Sahar Hashmi, MD, Robert A. Frankelstein, MD, Fahad Shuja, MD, Eugene Y. Fukudome, MD, Yongqing Li, MD, PhD, Baoling Liu, MD, Marc deMoya, MD, and George C. Velmahos, MD, PhD

The Journal of **TRAUMA**® *Injury, Infection, and Critical Care* • Volume 68, Number 5, May 2010

Hypothermia and hemostasis in severe trauma: A new crossroads workshop report

Hasan B. Alam, MD, Anthony E. Pusateri, PhD, Andrei Kindzelski, MD, PhD, Debra Egan, MPH, Keith Hoots, MD, PhD, Matthew T. Andrews, PhD, Peter Rhee, MD, MPH, Samuel Tisherman, MD, Kenneth Mann, PhD, Jaroslav Vostal, MD, PhD, Patrick M. Kochanek, MD, Thomas Scalea, MD, Virgil Deal, MD, Forest Sheppard, MD, George Sopko, MD, MPH,
***and* on behalf of the HYPOSTAT workshop participants,** *Boston, Massachussets*

October 2012

Sponsored by the NIH and the DoD

Guidelines for future research

Emergency Preservation and Resuscitation (EPR) for Cardiac Arrest From Trauma (EPR-CAT)

This study is not yet open for participant recruitment.

Verified August 2011 by University of Pittsburgh

Sponsor:
University of Pittsburgh

Collaborators:
University of Maryland
University of Pennsylvania
Massachusetts General Hospital
University of Arizona
Oregon Health and Science University

Information provided by:
University of Pittsburgh

ClinicalTrials.gov Identifier:
NCT01042015

First received: January 4, 2010
Last updated: August 2, 2011
Last verified: August 2011
History of Changes

Goals of early trauma care

- Keep alive
- Minimize organ injury
- Decrease bleeding

- Keep alive
- Preserve key organs
- ABC's

- Fix injuries
- Resuscitate
- Support organs

Pre-hospital → **ED** → **OR/SICU**

Pro-survival drugs

Freeze dried plasma

EPR

The difficulty lies, not in the new ideas,

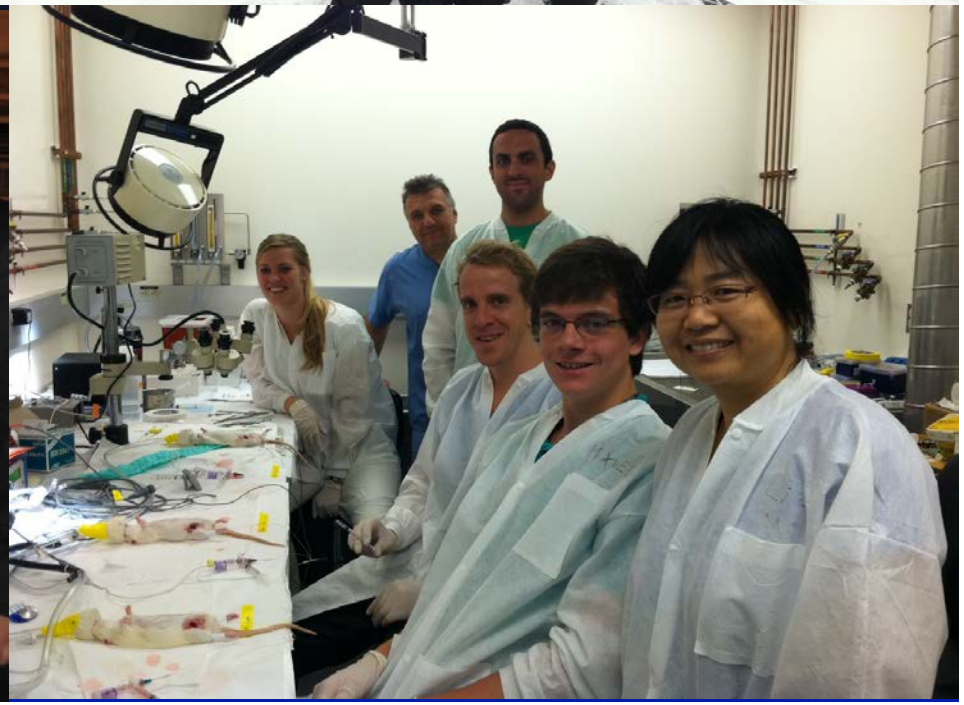
but in escaping from the old ones..

John Maynard Keynes (1883-1946)

Key points

- Identify need- area of investigation
- Think big
- Mentors
- Collaborators
- Mentees
- Scheduled writing
- Marry the right person

Families



Funding acknowledgement:
National Institutes of Health and US
Department of Defense