Safar Center for Resuscitation Research:

Novel Approaches in Resuscitation and Therapy of Blast TBI and Polytrauma

ATACCC 2009

Patrick M. Kochanek, MD
Director, Safar Center
Professor and Vice Chairman
Dept. of Critical Care Medicine
Professor, Depts. Of Anesthesiology and Pediatrics

SAFAR CENTER FOR RESUSCITATION RESEARCH
UNIVERSITY OF PITTSBURGH

Safar Center Current Research

www.safar.pitt.edu

Resuscitation Medicine and Science from the Field to Rehabilitation

Requiring Resuscitation

t: US Army, DARPA, NDS and NICHD) aerdal Foundation

Clinical Research & Experimental Models of Critical Injury that Closely Mimic the Clinical Condition

Brain Injury

Cardiac Arrest

Hemorrhagic Shock & Polytrauma

"EMERGENCY PRESERVATION & RESUSCITATION" (EPR)

Child Abuse

Blast Injury

Neurointensive Care

Some of the current funded TBI projects at the Safar Center:

- Therapeutic hypothermia bench to bedside
- Novel TBI resuscitation
- Autophagy in TBI
- Oxidative & nitrative stress and oxidative lipidomics in CNS injury
- Adenosine and cAMP in TBI
- Calcineurin in TBI
- Dopamine signaling in TBI therapy and rehabilitation
- Enriched environment in TBI recovery
- Biomarkers in child abuse and pediatric neurointensive care
- CBF promotion in cerebral resuscitation after cardiac arrest
- Extracorporeal resuscitation after cardiac arrest
- Emergency preservation and resuscitation
- P-glycoprotein transporters in TBI therapy
- Novel findings in blast TBI
- Drug screening for blast TBI and polytrauma

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Safar Center DOD Interface Current-TBI

Safar Center TBI Program

Novel Nitroxide-based TBI resuscitation
Peer-reviewed medical research program
P. Kochanek, MD, PI

PREVENT blast program
Phase II
DARPA
Richard Bauman, PhD, PI
COL Geoff Ling, MD, Program Manager
P. Kochanek, MD Site PI

Calcineurin and TBI
Veterans Administration
C. Edward Dixon, PhD, PI

Biomarkers in TBI
CDMRP Concept award
Amy Wagner, MD

Oxygen and ventilation in TBI resuscitation
CDMRP
COL James Atkins, PhD, PI
Joseph Long, PhD, Co-I
Gary Fiskum, PhD, U. Maryland Site PI
P. Kochanek, MD Pittsburgh, Site PI

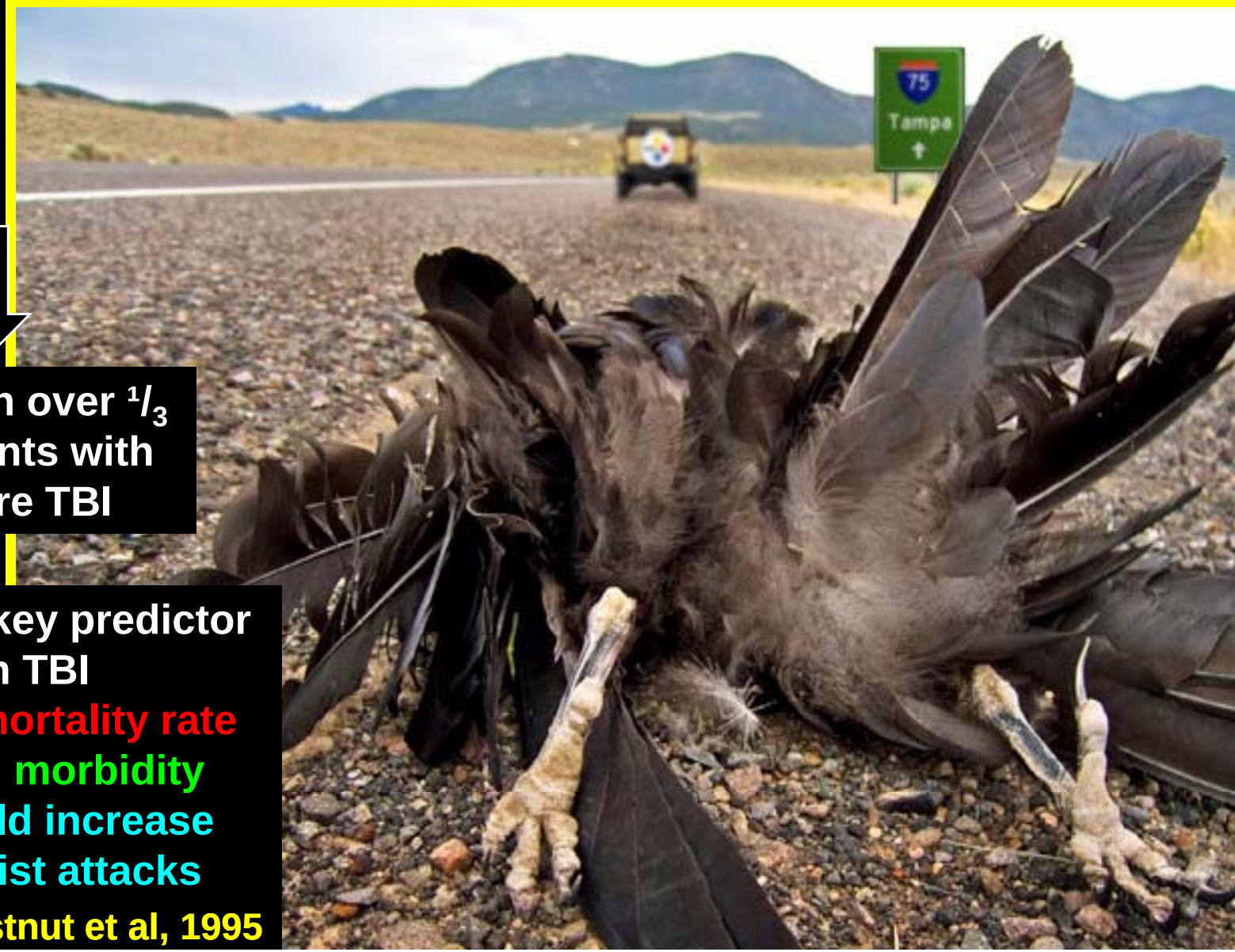
New Findings

Critical role of hypotension/shock in producing poor outcome after traumatic brain injury

2° insult

Hypotension

Occurs in over $^{1}/_{3}$ of patients with severe TBI



- Hypotension—a key predictor of poor outcome in TBI
- Doubles/triples mortality rate
- Large increase in morbidity
- This problem could increase further with terrorist attacks

Chestnut et al, 1995

PERSPECTIVE

NOTES OF A SURGEON

Casualties of War — Military Care for the Wounded from Iraq and Afghanistan

Atul Gawande, M.D., M.P.H.

IEDs…often combine penetrating, blunt, and burn injuries

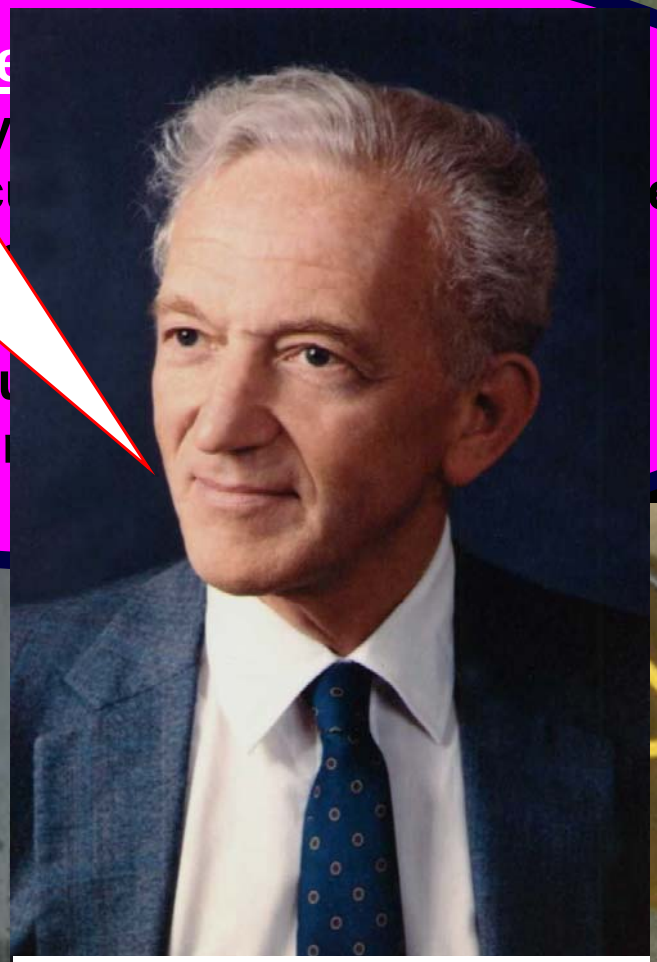
The shrapnel include.….nails, bolts, and the like.…

Victims can exsanguinate from multiple seemingly small wounds…

Experimental Traumatic Brain Injury Models at Safar Center: Controlled Cortical Impact Model

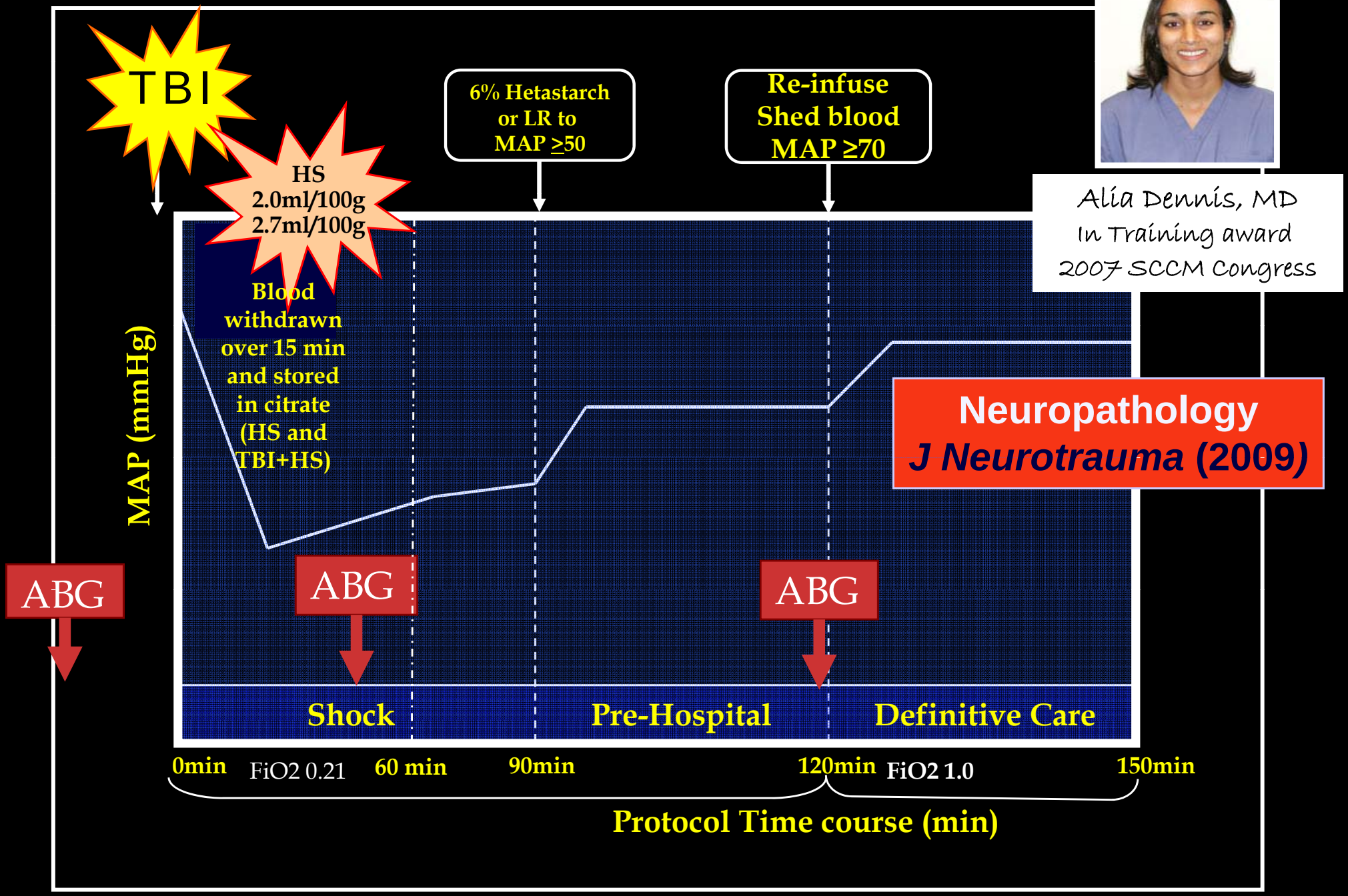
CE Dixon, PhD

Mimic the clinical condition as closely as possible – bring the Field/ED & ICU to the bench



The late Peter Safar

Lighthall et al, 1998
Dixon et al, 1991


TBI
HS
2.0ml/100g
2.7ml/100g
6% Hetastarch
or LR to
MAP ≥50
Re-infuse
Shed blood
MAP ≥70
Blood
withdrawn
over 15 min
and stored
in citrate
(HS and
TBI+HS)
MAP (mmHg)
ABG
ABG
ABG
Shock
Pre-Hospital
Definitive Care
0min
FiO2 0.21
60 min
90min
120min
FiO2 1.0
150min
Protocol Time course (min)
Alia Dennis, MD
In Training award
2007 SCCM Congress
Neuropathology
J Neurotrauma (2009)

Methods

Anesthetized
4% Isoflurane, N2O/O2 [2:1]

2% Isoflurane

Femoral Artery and Vein Cannulation
(BP, sampling, hemorrhage)

Burr hole with microtemp
Tbrain = 37±0.5°C

1.5% Isoflurane

Randomization to treatment groups

CCI | **HS60** | **HS90** | **CCI+HS60** | **CCI+HS90**

Left Parietal Craniotomy
(HS60 & HS90 exempt)

10 min
1% Isoflurane, room air

CCI

5mm tip; 5m/s velocity; 1mm depth
(HS60 & HS90 exempt)

5 min

Hemorrhagic Shock

No Shock (CCI)

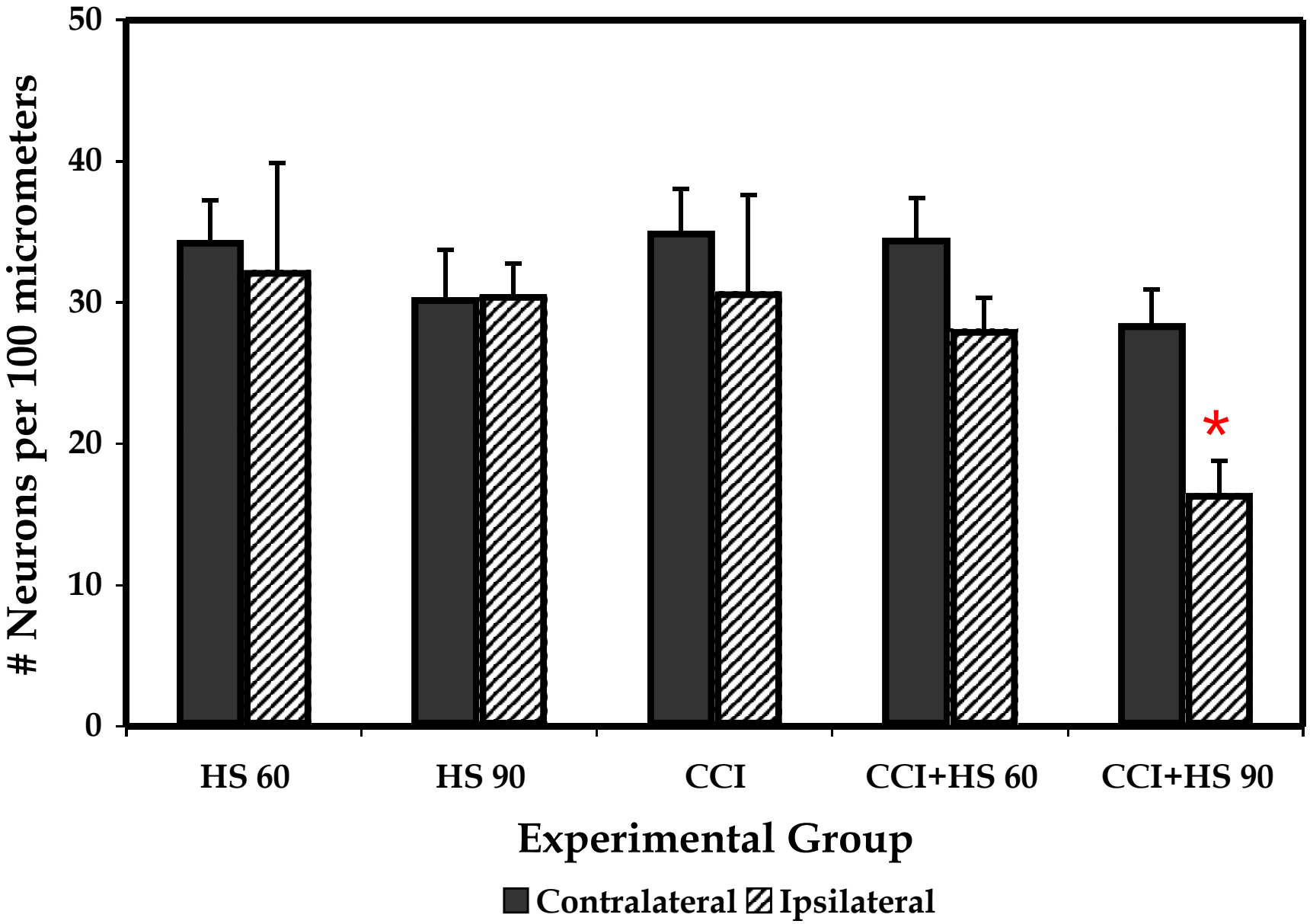
60 min
(HS60 & CCI+HS60)

90 min
(HS90 & CCI+HS90)

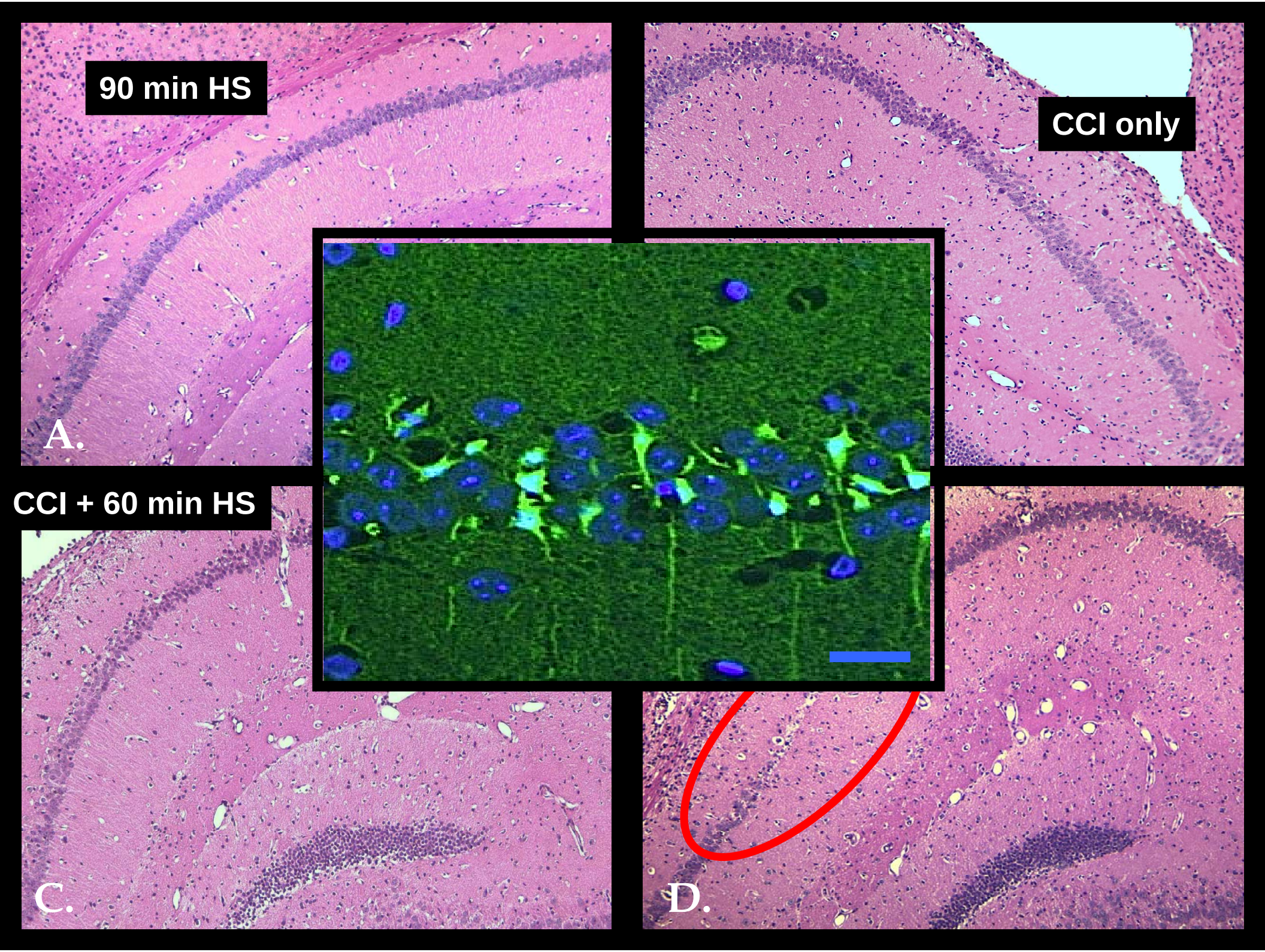
Table 1. Physiologic data (Mean arterial blood pressure, hematocrit, arterial lactate, and arterial base excess)

		Baseline	Shock	Definitive Care
MAP	CCI only	85.4 ± 6.6	80.2 ± 4.0	77.0 ± 2.5
	60 HS only	90.2 ± 3.6	35.5 ± 3.6	74.5 ± 5.4
	90 HS only	89.8 ± 5.3	39.3 ± 4.1	72.8 ± 4.3
	60 CCI+HS	88.5 ± 8.4	34.3 ± 5.0	69.9 ± 5.0
	90 CCI+HS	85.4 ± 5.5	36.3 ± 6.4	69.9 ± 6.9
HCT	CCI only	38.7 ± 4.6	36.3 ± 4.5	32.4 ± 4.3
	60 HS only	36.6 ± 1.4	27.6 ± 1.8	30.1 ± 1.9
	90 HS only	35.7 ± 1.1	26.6 ± 1.7	29.3 ± 1.8
	60 CCI+HS	37.1 ± 3.7	27.7 ± 3.7	28.5 ± 2.4
	90 CCI+HS	36.8 ± 2.6	28.3 ± 2.0	28.3 ± 2.0
Lactate	CCI only	2.5 ± 0.1	2.4 ± 0.3	1.8 ± 0.2
	60 HS only	2.2 ± 0.1	4.0 ± 0.4	1.6 ± 0.1
	90 HS only	2.3 ± 0.1	3.2 ± 0.2	1.6 ± 0.1
	60 CCI+HS	2.6 ± 0.2	3.5 ± 0.3	1.9 ± 0.2
	90 CCI+HS	2.5 ± 0.2	4.2 ± 0.4	2.2 ± 0.1
Base Excess	CCI only	-4.7 ± 0.4	-5.2 ± 0.4	-5.7 ± 1.5
	60 HS only	-4.7 ± 0.7	-6.9 ± 0.4	-4.8 ± 0.2
	90 HS only	-4.7 ± 0.3	-6.6 ± 0.2	-5.4 ± 0.4
	60 CCI+HS	-4.7 ± 0.3	-8.1 ± 0.6	-4.9 ± 0.5
	90 CCI+HS	-4.7 ± 0.4	-7.2 ± 0.3	-5.1 ± 0.5

CA1 –surviving neurons at 7 d

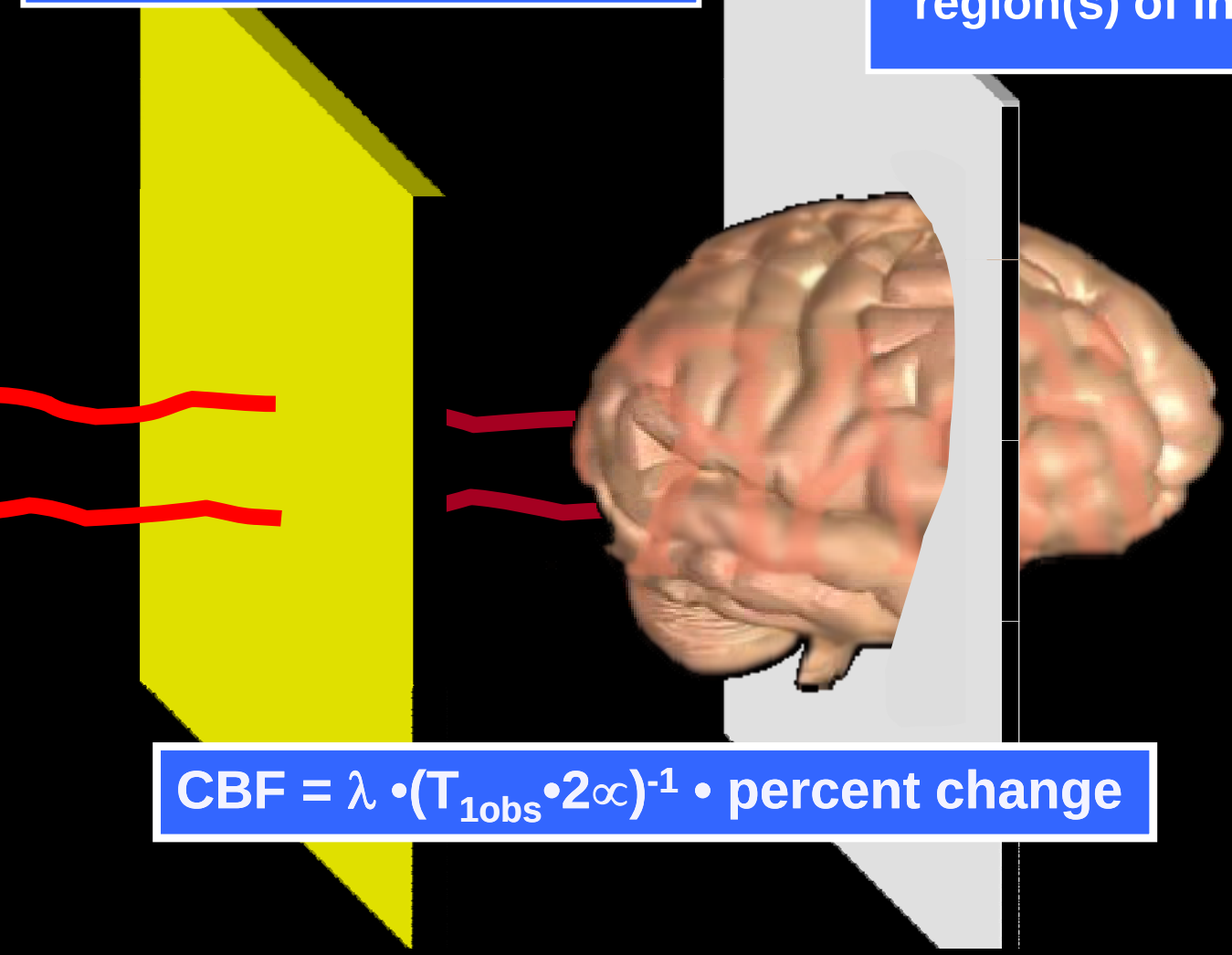


J Neurotrauma (June, 2009)


90 min HS
A.
CCI only
CCI + 60 min HS
C.
D.

Radio-frequency labeling of water molecules in carotid arteries

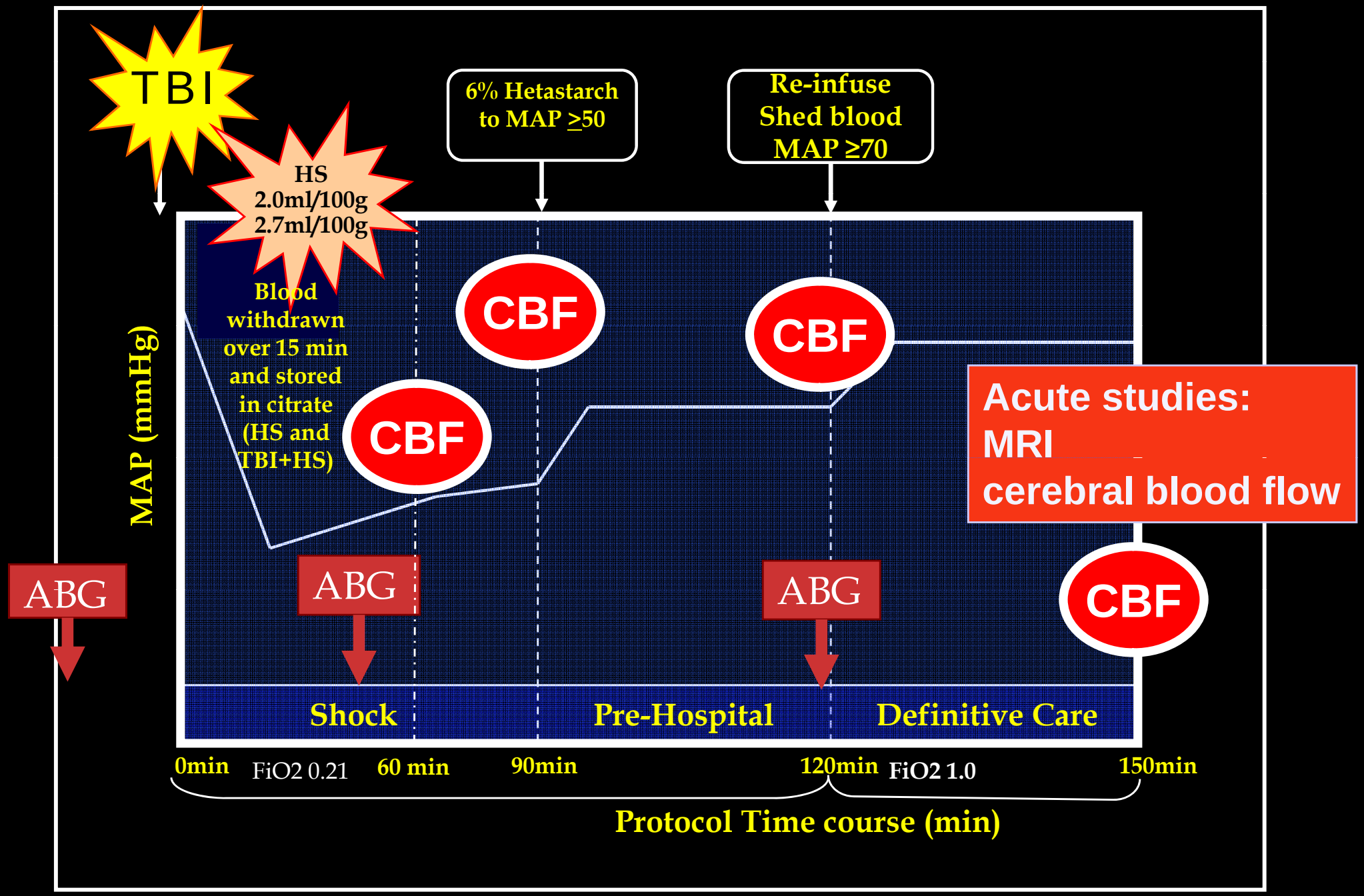
Imaging through coronal section within region(s) of interest



$$CBF = \lambda \cdot (T_{1obs} \cdot 2\propto)^{-1} \cdot \text{percent change}$$

Mouse MRI:
Bruker AVANCE BioSpin MRI
4.7 Tesla Magnet

Arterial Spin - Labeled Magnetic Resonance Imaging Assessment of Cerebral Blood Flow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to MAP ≥50
Re-infuse
Shed blood
MAP ≥70
Blood
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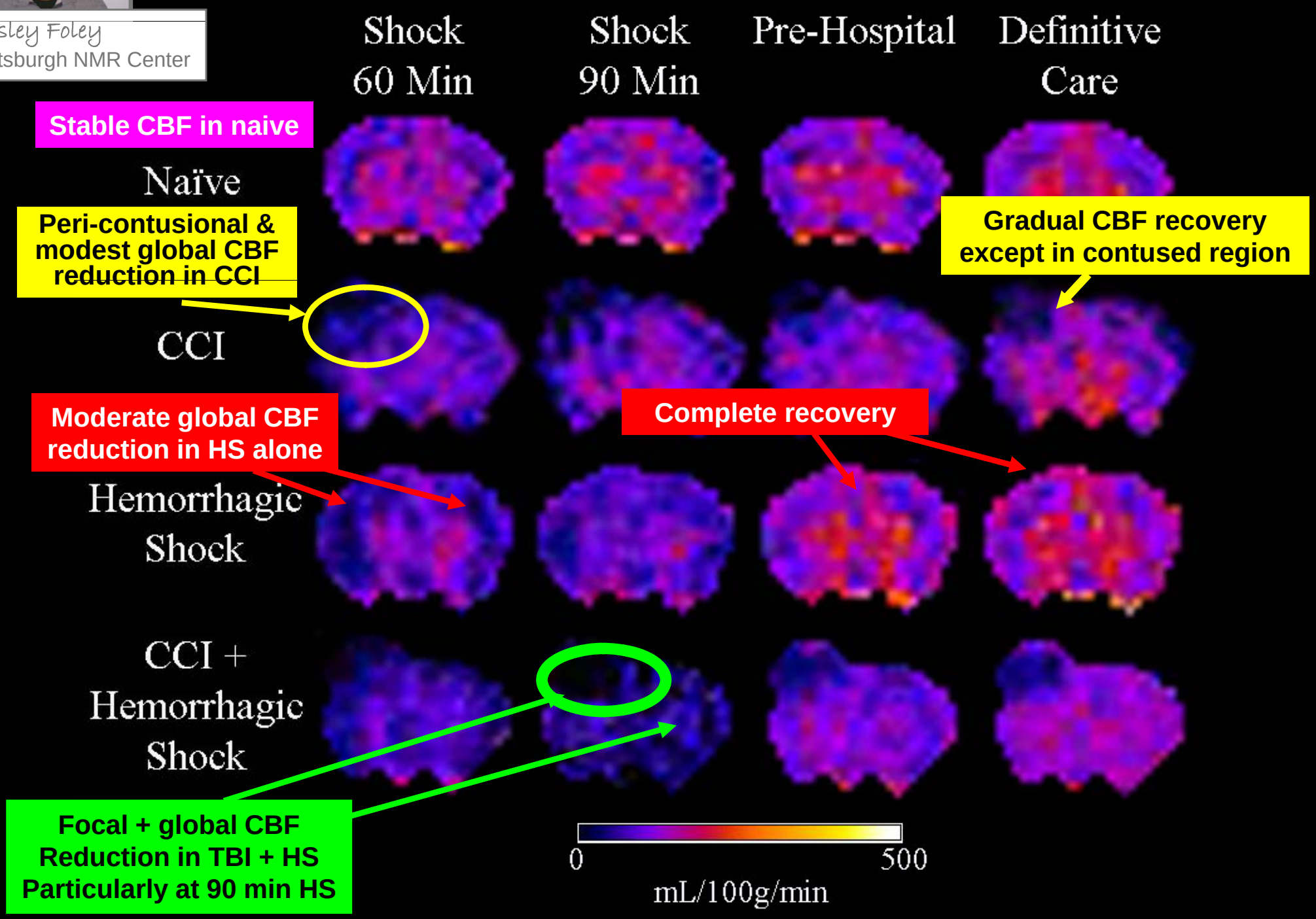
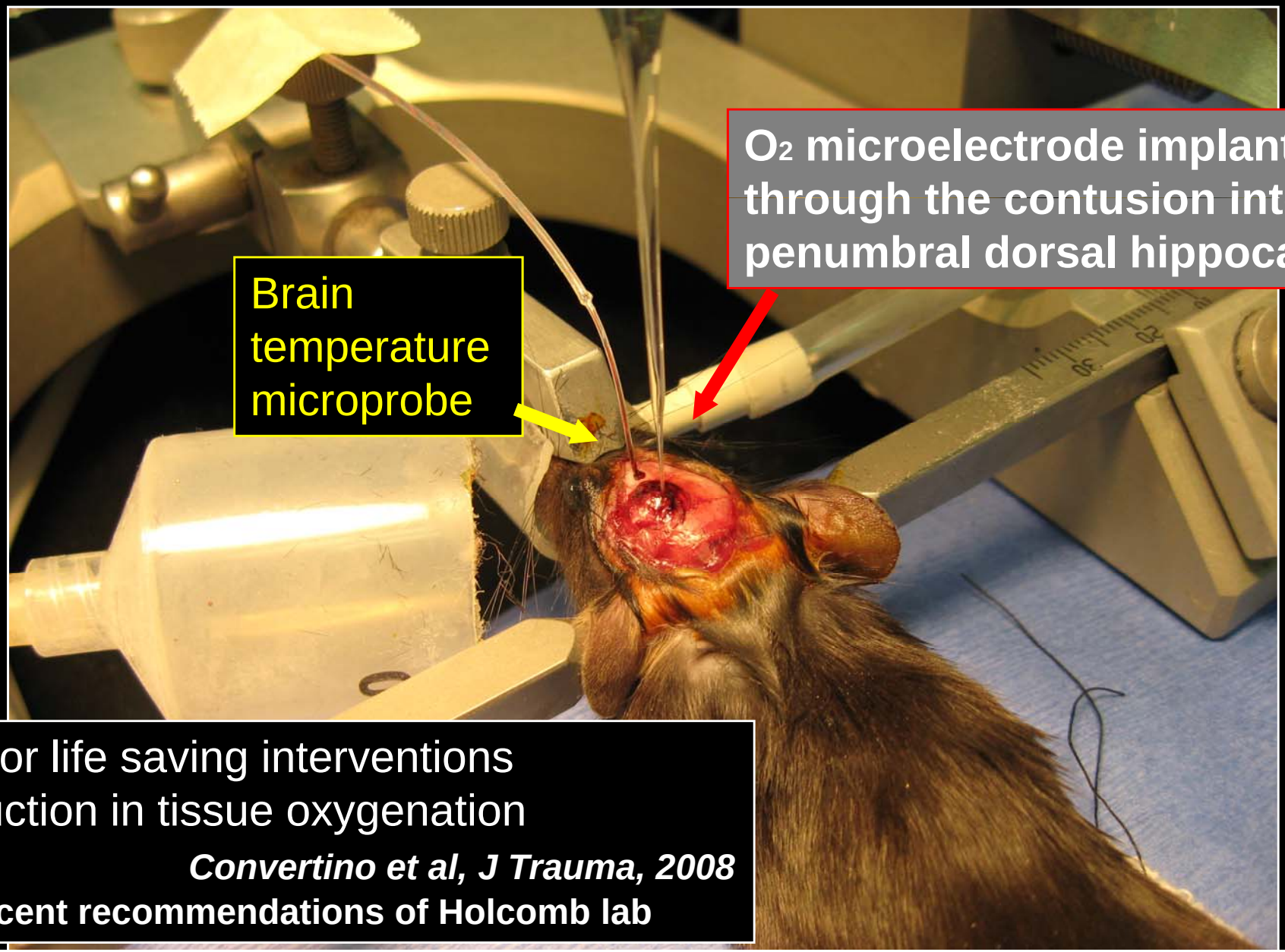
over 15 min
and stored
in citrate
(HS and
TBI+HS)
CBF
CBF
CBF
CBF
Acute studies:
MRI
cerebral blood flow
MAP (mmHg)
ABG
ABG
ABG
Shock
Pre-Hospital
Definitive Care
0min
FiO2 0.21
60 min
90min
120min
FiO2 1.0
150min
Protocol Time course (min)

Lesley Foley
Pittsburgh NMR Center

CBF maps of the Effect of Hemorrhagic Shock after TBI in Mice



Brain Tissue O_2 Monitoring after Combined TBI + HS in Mice



Need for life saving interventions
--Reduction in tissue oxygenation

Convertino et al, J Trauma, 2008

Most recent recommendations of Holcomb lab

THERAPY

- **Blood substitutes**
- **Resuscitation fluids**
- **Resuscitation strategies**
- **FDA-approved therapies**
- **Novel neuroprotective agents**

THERAPY

There is no better resuscitation fluid for a critically injured bleeding TBI victim than fresh whole blood…

- Not available in the field
- Storage and transport
- Safety
- Dosing

What about an artificial Hemoglobin?
HBOC = hemoglobin based oxygen carrier

First Generation Blood Substitutes

16 studies

3000+ patients

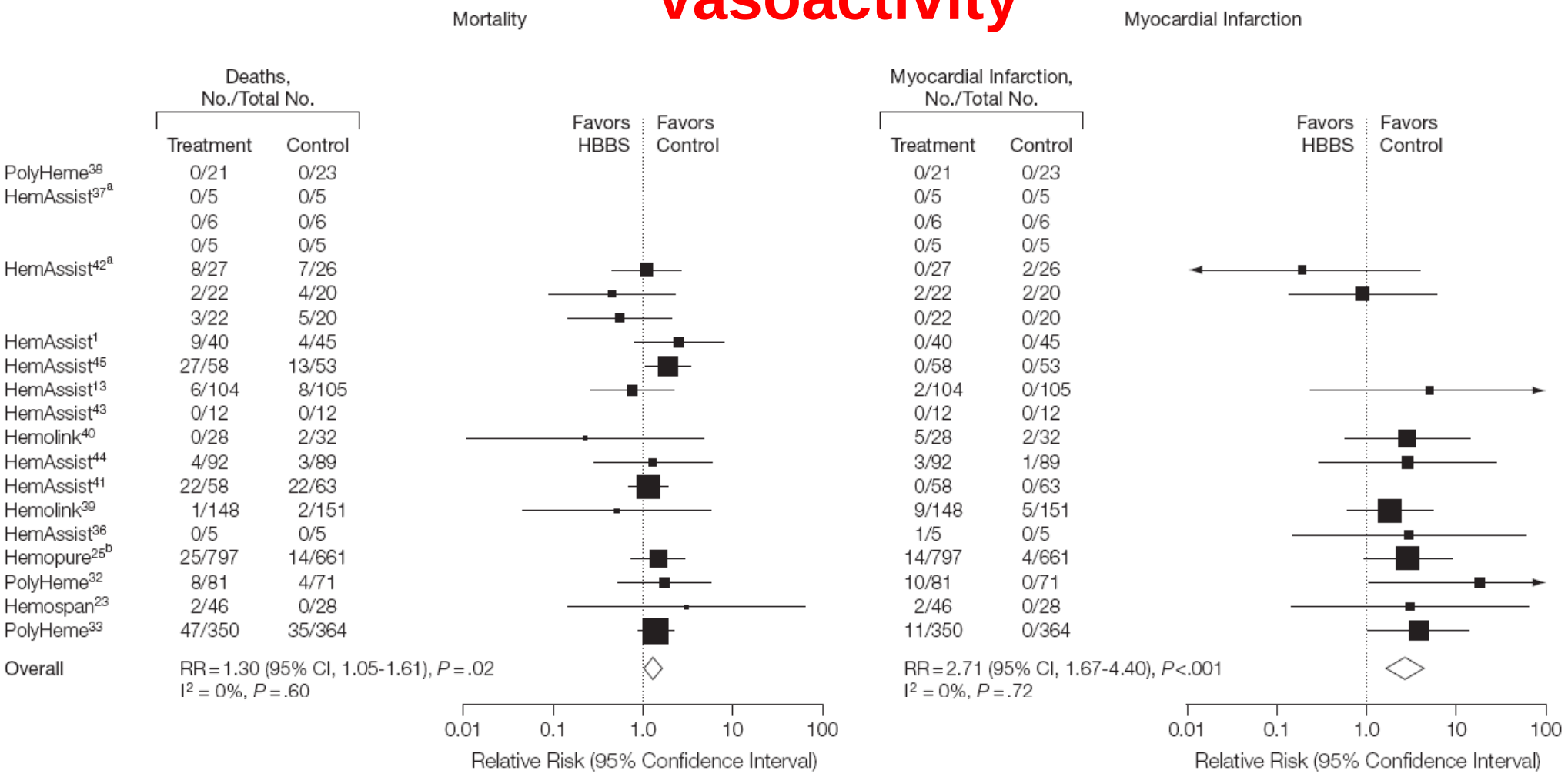
Cell-Free Hemoglobin-Based Blood Substitutes and Risk of Myocardial Infarction and Death: A Meta-analysis

Charles Natanson; Steven J. Kern; Peter Lurie; et al.

JAMA. 2008;299(19):2304-2312 (doi:10.1001/jama.299.19.jrv80007)

Figure 2. Mortality and Myocardial Infarction

"Vasoactivity"



Controversy over the key factor involved in free Hb-mediated "vasoactivity"

NO consumption

Modify Hb to limit NO consumption

Normal or high P_{50} to enhance tissue delivery

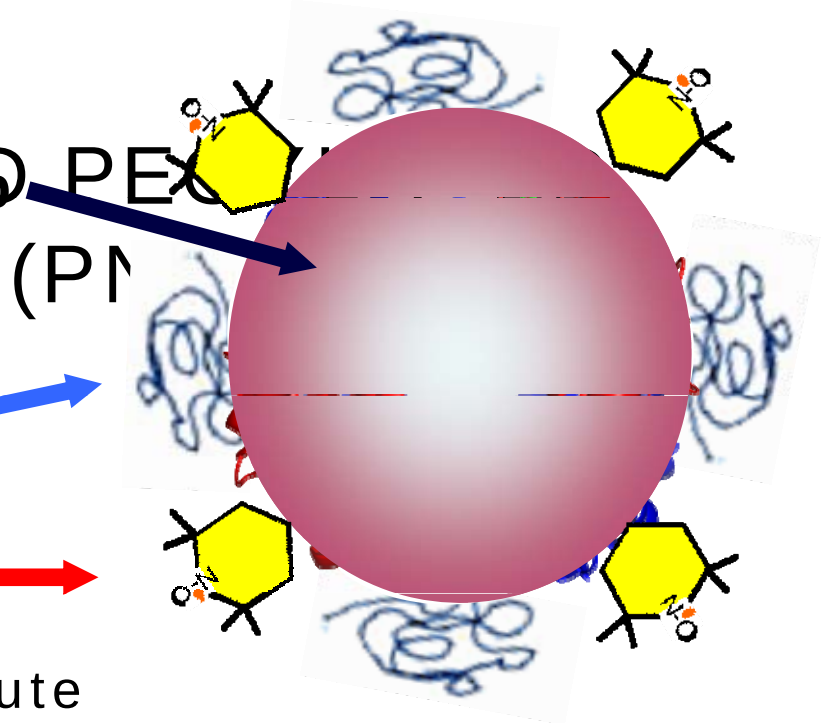
Excessive O_2 delivery (autoregulation theory)

Winslow et a, 2003

Limit P_{50} to prevent excess tissue delivery

Modify Hb to limit NO consumption

POLYNITROXYLATED PEGYLATED HEMOGLOBIN (PNPH)



Second-Third generation blood substitute

- Nitroxide moieties (n=14) may attenuate secondary injury
  - Antioxidant effects (recycling effect)
  - SOD and catalase-mimetic
  - Limit the ability of superoxide to react and deplete NO
- PEG moieties (n=8-10); MW 5000; a low P50 (11)
  - Oncotic effects enhancing plasma expansion
  - Increases T1/2 by reducing proteolysis and glomerular filtration
  - Reduces immunogenicity
  - Viscous “drag” of PEG stimulates endothelial NOS
  - Theoretical “pseudothiol” effect of PEG--NO reservoir

Nitroxides are beneficial in experimental TBI

Free Radical Biology & Medicine, Vol. 24, No. 2, pp. 332–340, 1998
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ELSEVIER

Original Contrib

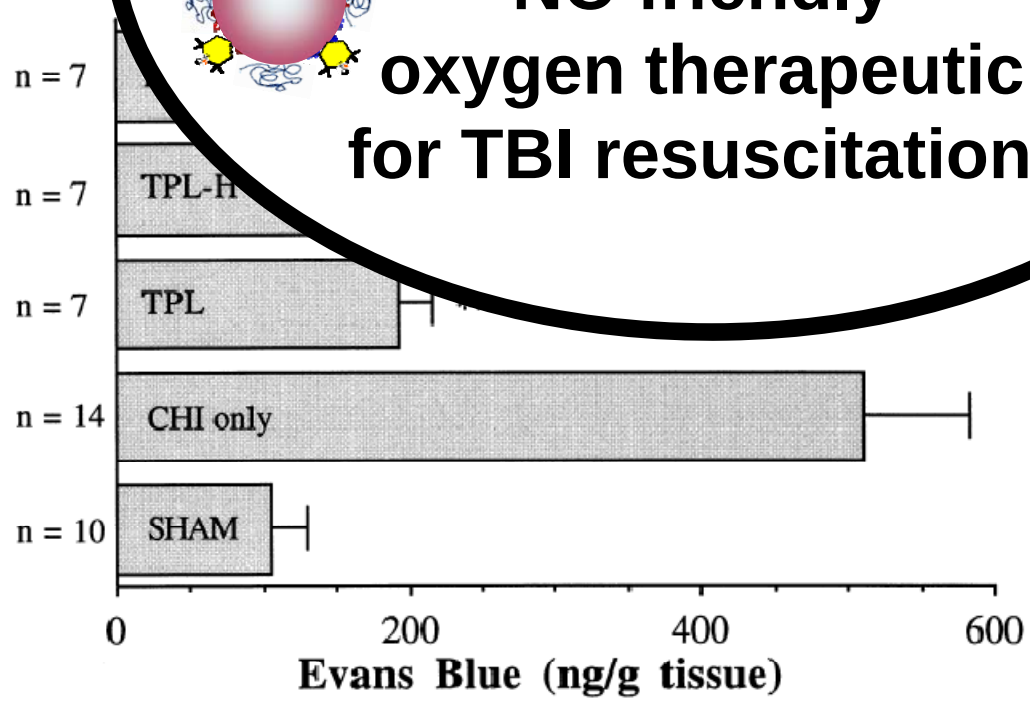
MECHANISM
EX

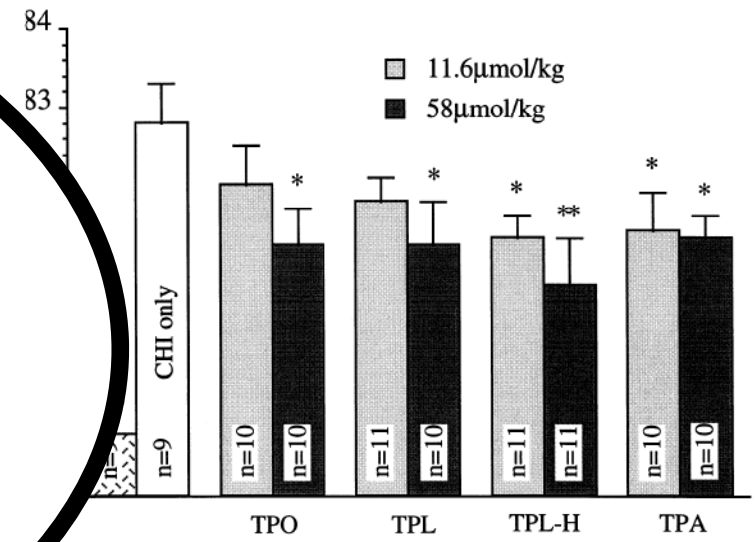
RENLIANG Z

*Departme

PNPH

A potentially useful small volume NO friendly oxygen therapeutic for TBI resuscitation?





2. Reduction by nitroxides and TPL-H of brain edema in rats subjected to CHI. The nitroxides TPA, TPL, and TPO, as well as the hydroxylamine TPL-H at either 58 μmol/kg or 11.6 μmol/kg were injected IV 5 min after CHI in rats. Control (CHI only) rats received saline. The brain edema at the contused hemisphere was assessed by measurement of water content 24 h after CHI. The data are presented as mean ± SEM (n = number of rats). $^{*}p < .05$ vs. control; $^{**}p < .01$ vs. control.

The nitroxide tempol attenuates edema and BBB damage after TBI in rats

Study 1

PNPH in TBI plus
Volume-Controlled Hemorrhagic shock

METHODS

Anesthetized
4% Isoflurane, N2O/O2

2% Isoflurane

Femoral Artery and Vein Cannulation
(BP, sampling, hemorrhage)

Burr hole with microtemp
Tbrain = 37±0.5°C

1.5% Isoflurane

Left Parietal Craniotomy

10 min
1% Isoflurane, room air

3mm tip; 5m/s velocity; 1mm depth

5 min

Hemorrhagic Shock Initiated (20 ml/kg)
Volume controlled HS

Randomization to treatment groups

LR

PNPH
4% solution

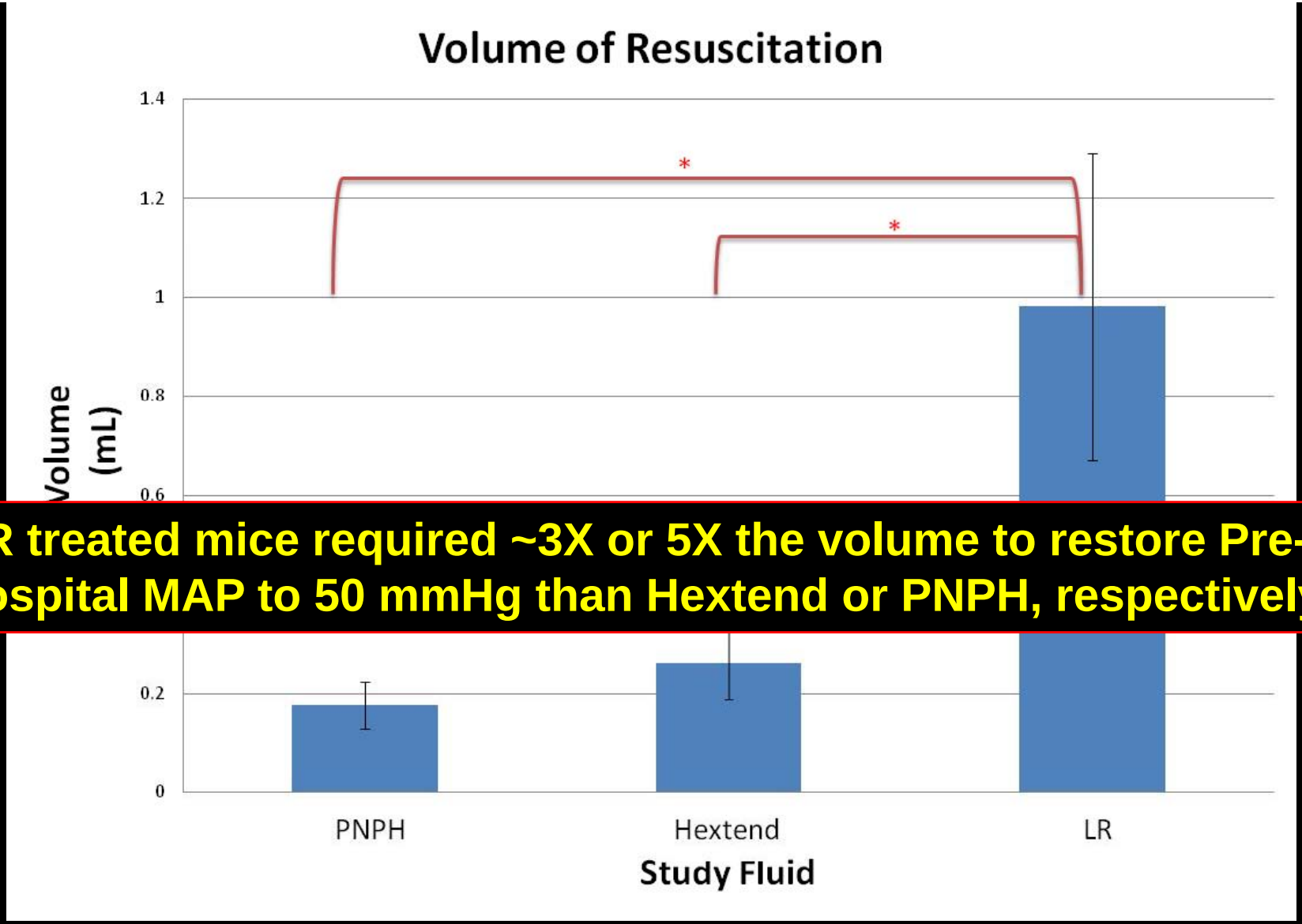
Hextend

C57 male mice

David Shellington, MD
Presented at the 2009 SCCM And 2009 NNT/INTS

Pre-hospital 50 mmHg
Definitive care 60 mmHg

PNPH is a Small Volume Resuscitation Fluid after TBI + HS

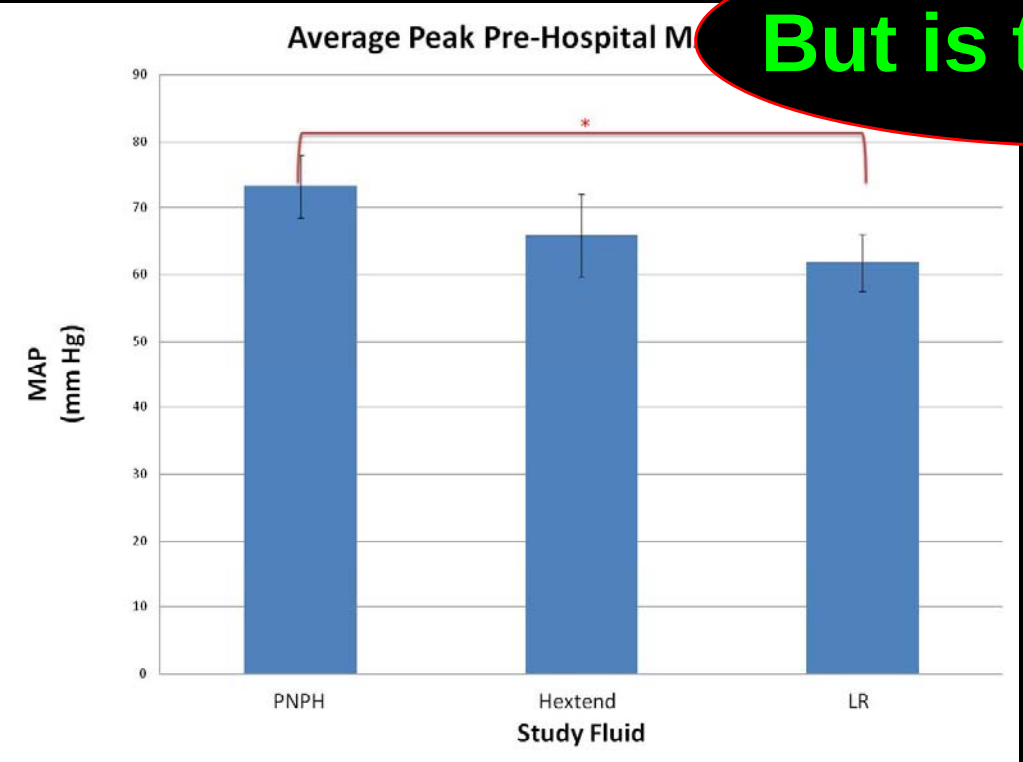


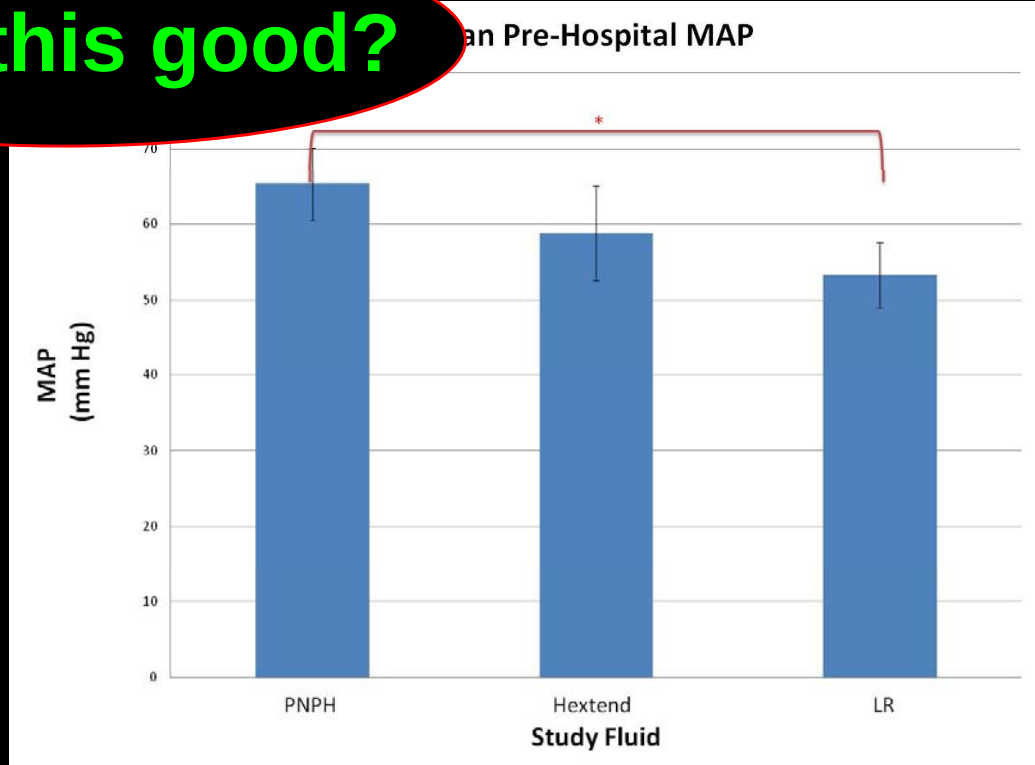
LR treated mice required ~3X or 5X the volume to restore Pre-hospital MAP to 50 mmHg than Hextend or PNPH, respectively

***P* < 0.05**

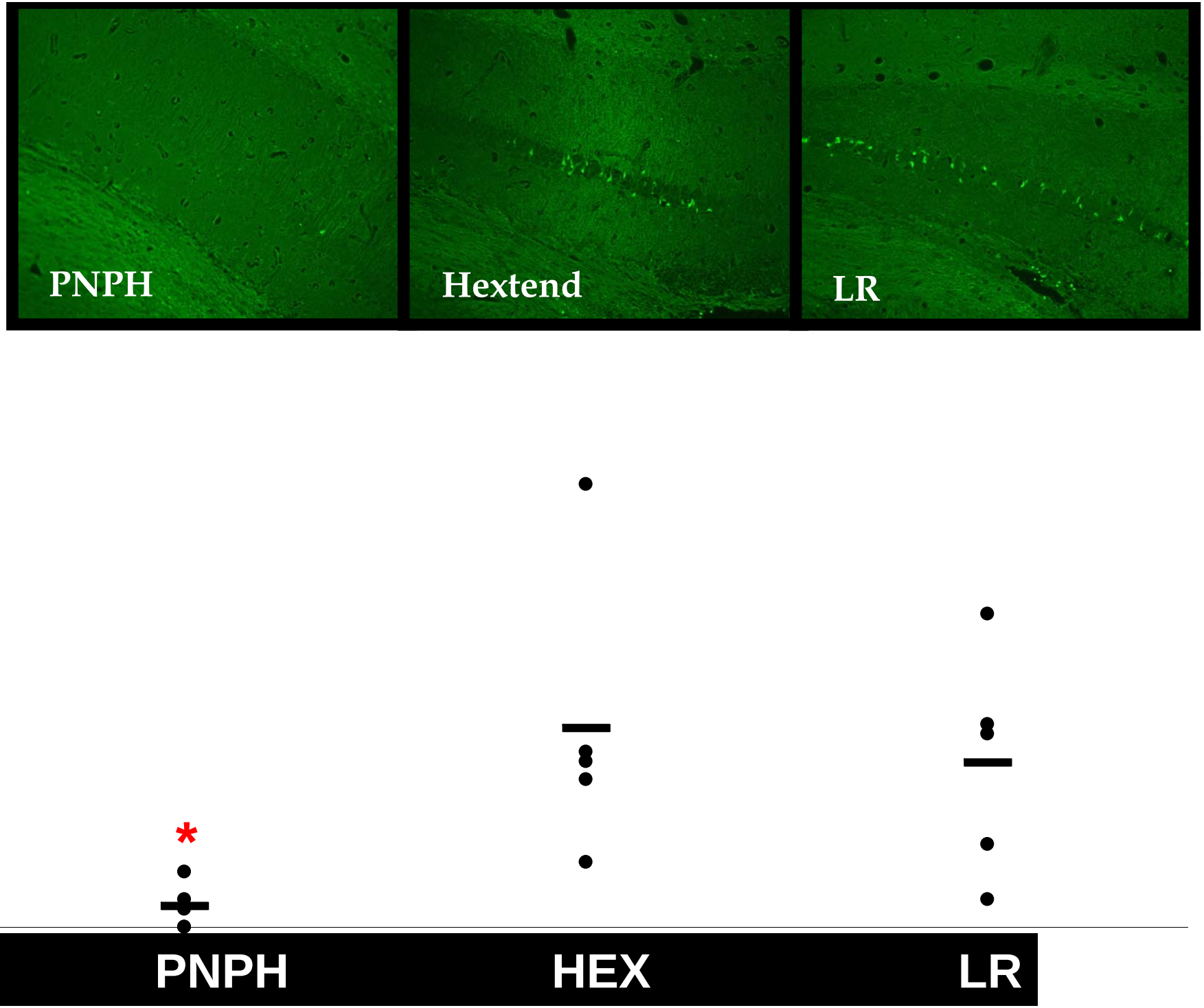
PNPH –MAP after TBI + HS

But is this good?



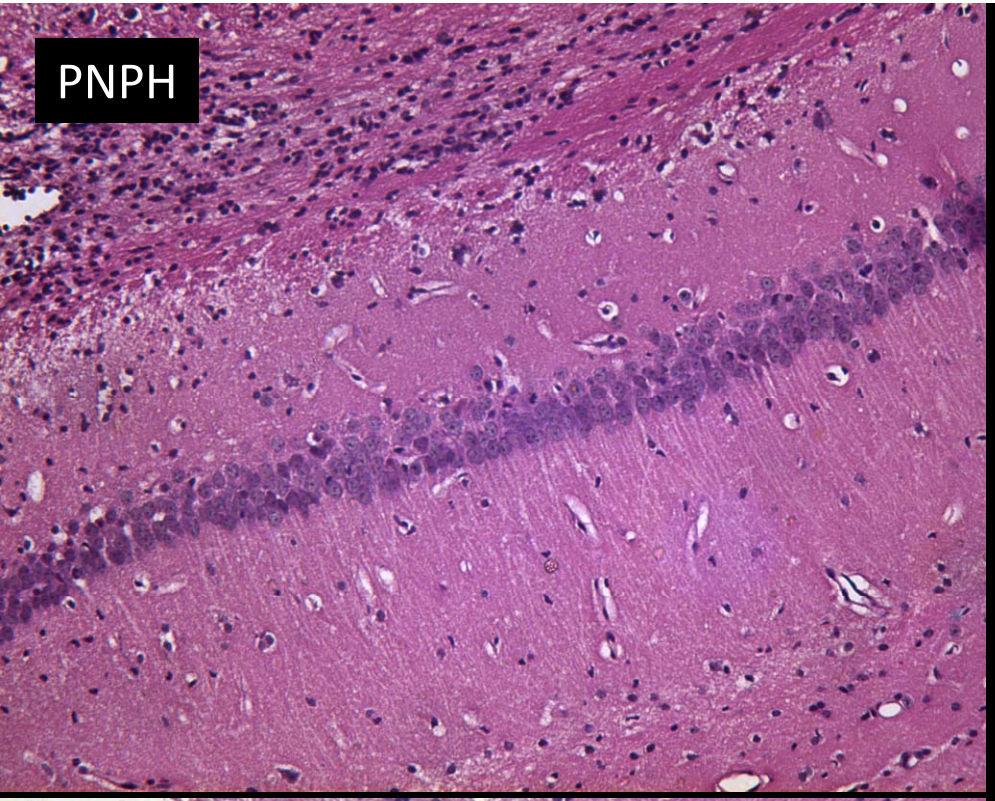


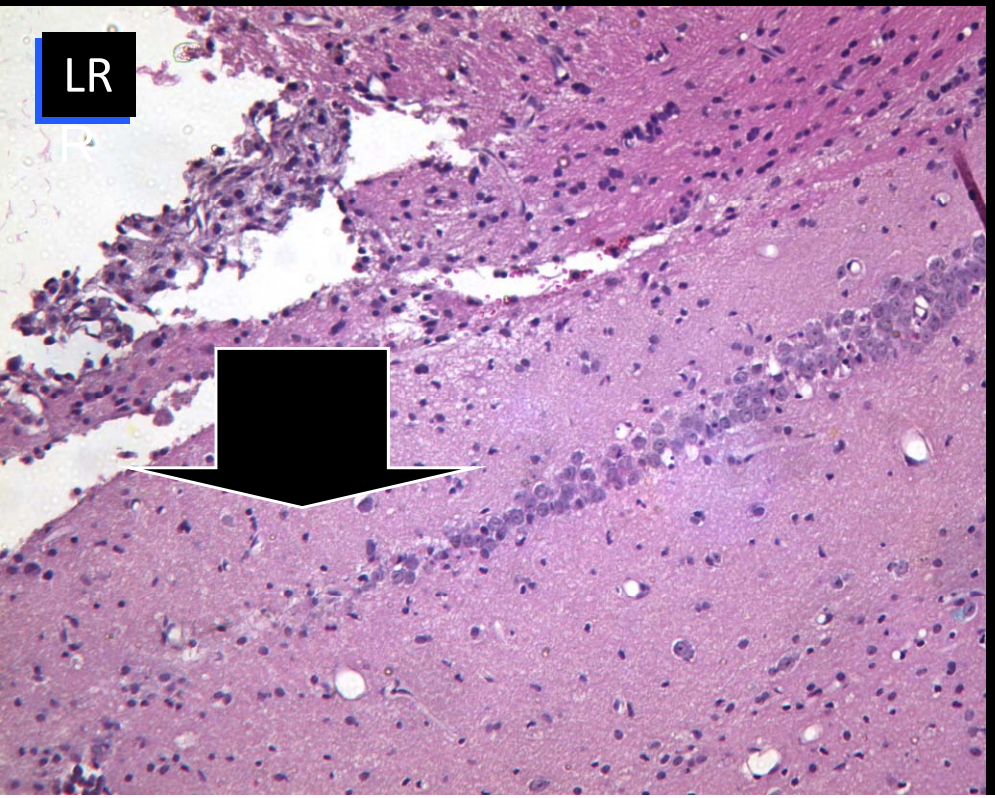
-treated mice achieved higher pre-hospital than either or extend treated mice—despite

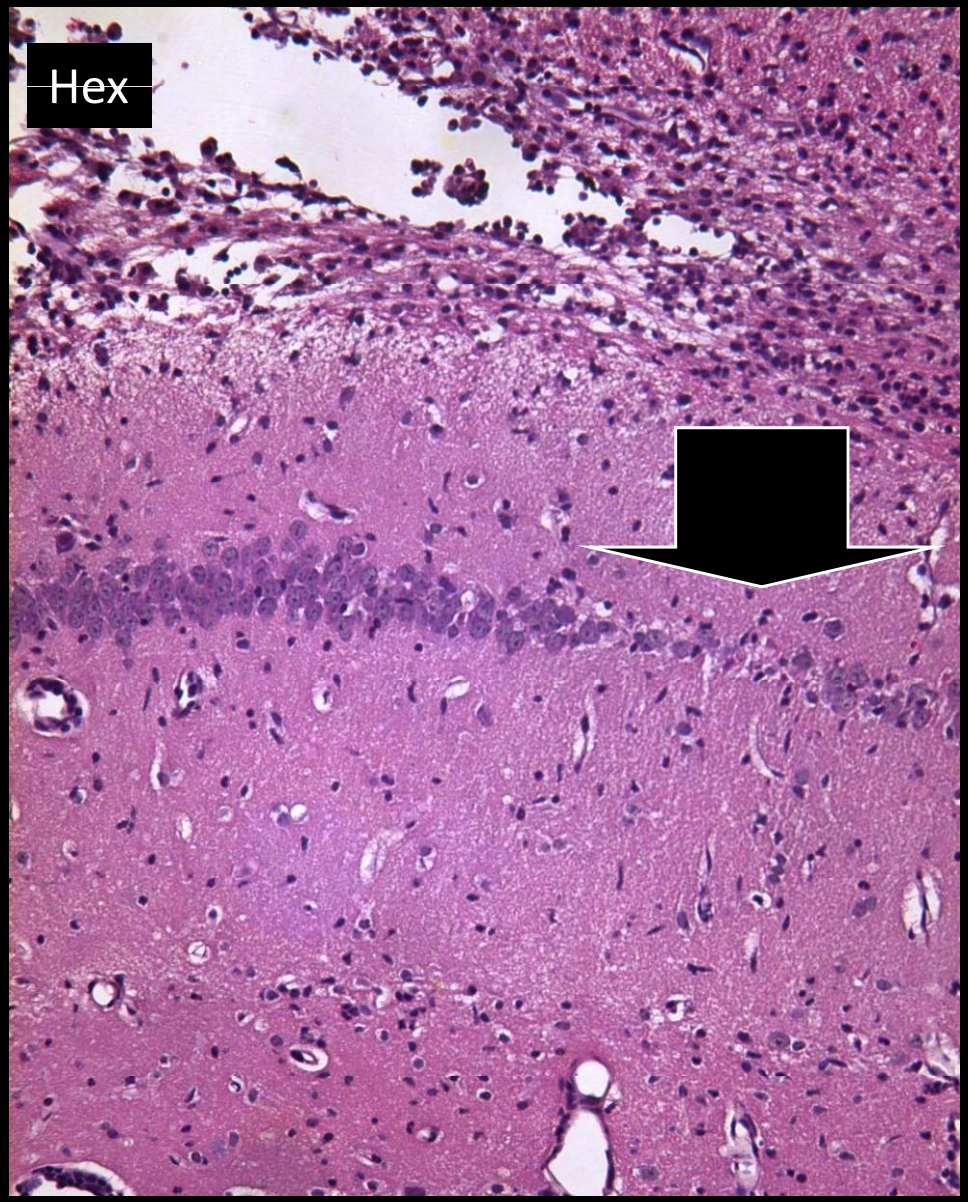


*P<0.05 vs HEX or LR

CA1 Histology of Mice Resuscitated with PNPH vs. LR and Hextend







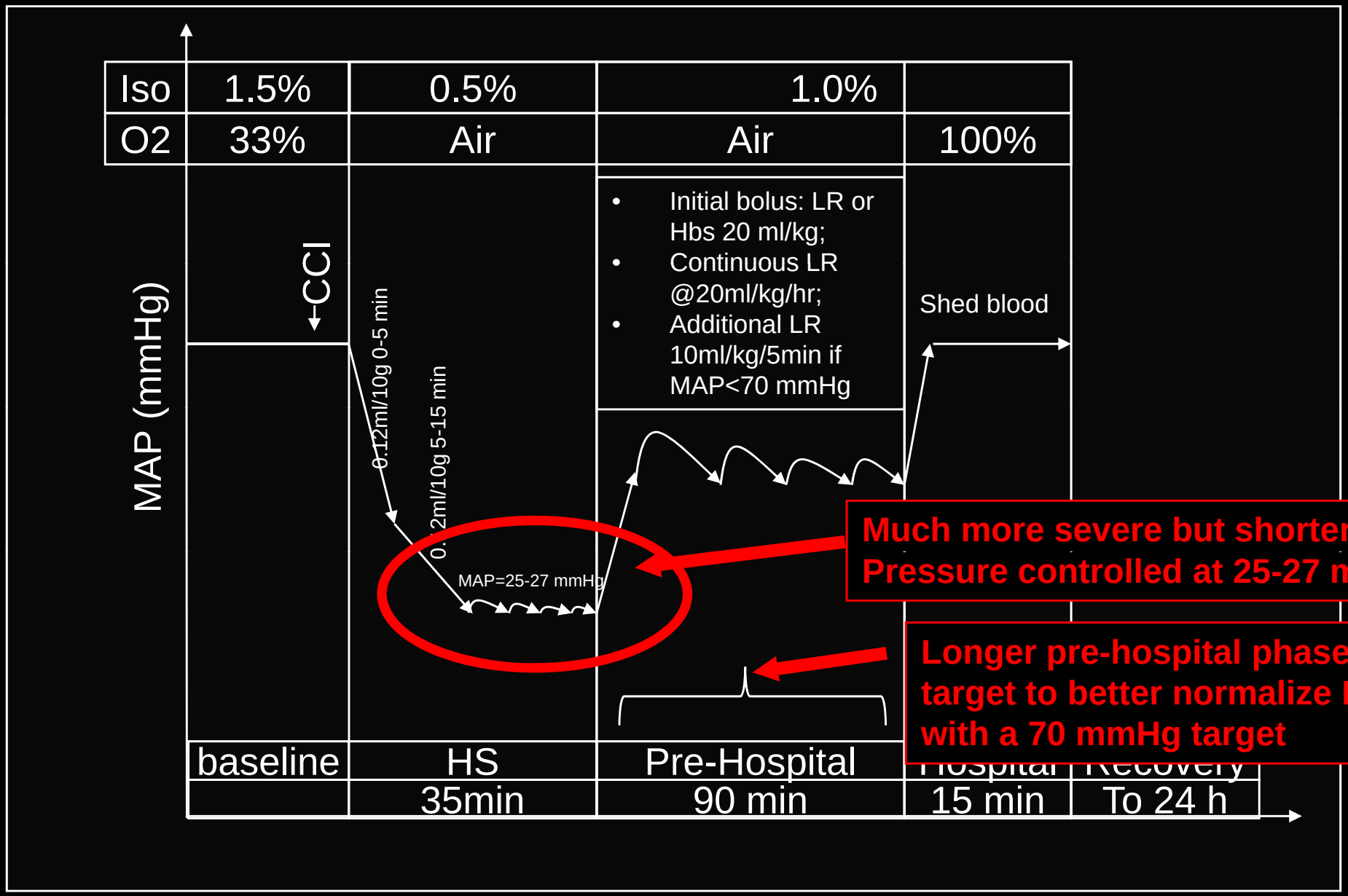
Xianren Wu, MD

Study 2

PNPH in TBI plus Pressure-Controlled Hemorrhagic shock

- PNPH vs LR
- Fluid requirements
- Hemodynamics
- Brain tissue oxygenation (hippocampal $PbtO_2$ probe)
- N=9 per group

TBI + pressure-controlled hemorrhagic shock



Much more severe but shorter HS
Pressure controlled at 25-27 mmHg

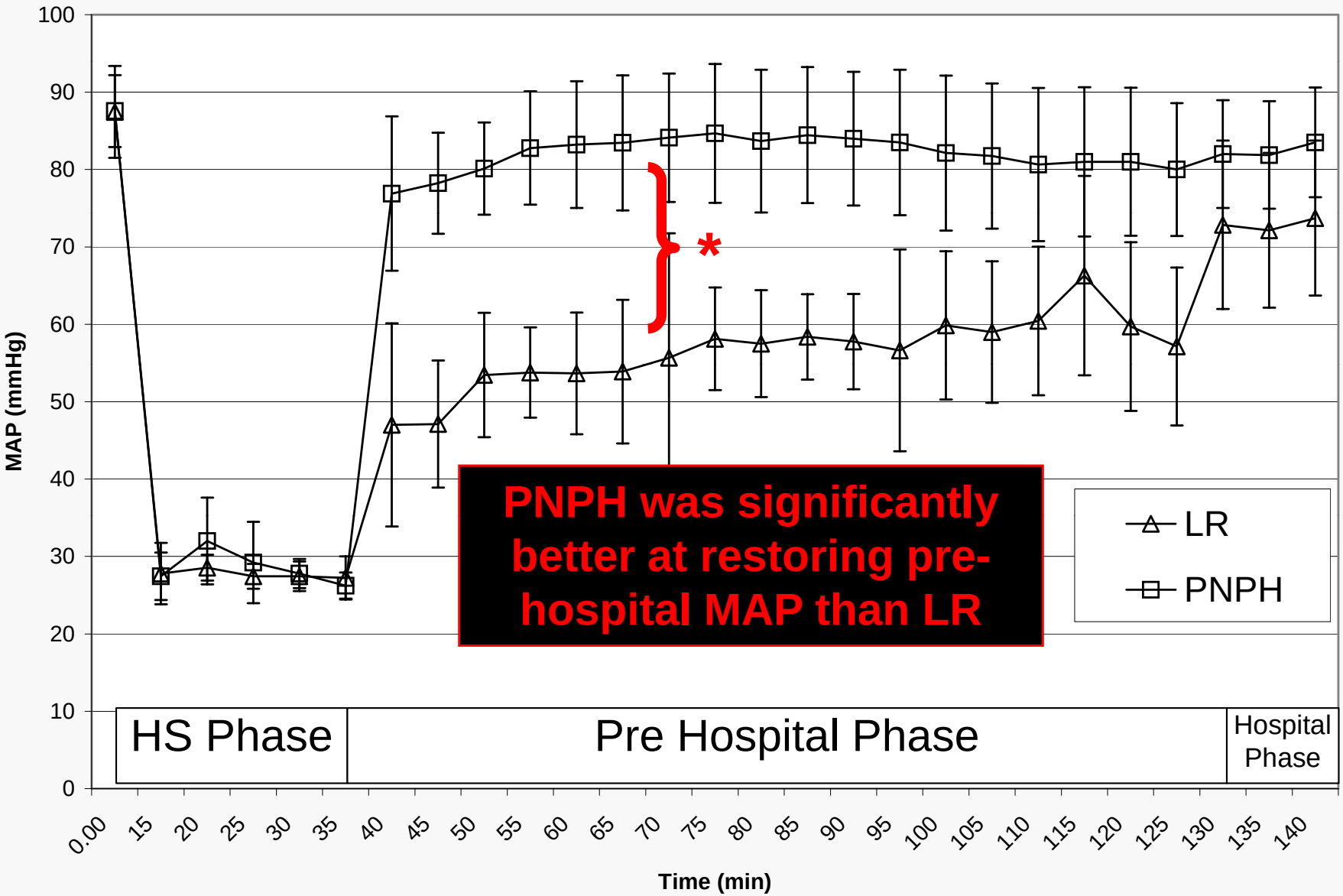
Longer pre-hospital phase; target to better normalize MAP with a 70 mmHg target

Fluid Requirements

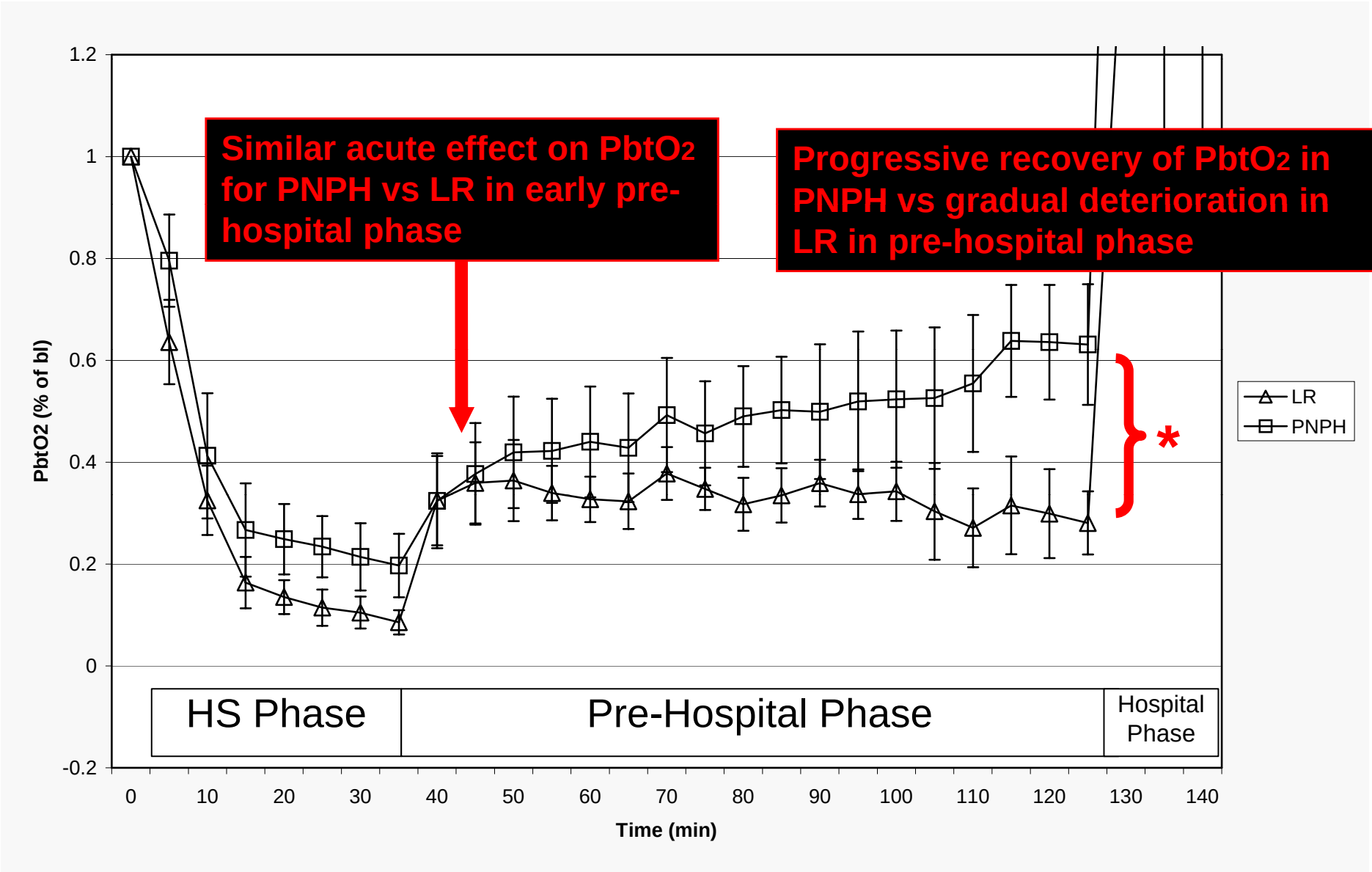
- LR group:
  - 205±20 ml/kg
- PNPH group:
  - 50±4 ml/kg (20 ml/kg PNPH + 30 ml/kg LR)

Highly significant difference in fluid requirements for MAP targets in pre-hospital phase between LR and PNPH

MAP


MAP (mmHg)
100
90
80
70
60
50
40
30
20
10
0
0.00
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
110
115
120
125
130
135
140
Time (min)
*
PNPH was significantly better at restoring pre-hospital MAP than LR
LR
PNPH
HS Phase
Pre Hospital Phase
Hospital Phase

Brain Tissue PO_2 ($PbtO_2$)



Arterial Blood Gases and other Physiological Parameters

	Baseline	End of HS	End of PP	End of HP
pH				
LR	7.43±0.03	7.35±0.06	7.39±0.04	7.33±0.07
PNPH(CO)	7.41±0.04	7.36±0.06	7.43±0.03	7.34±0.06
PO_2 (mmHg)				
LR	160.3±10.4	82.8±10.8	85.8±8.4	440.2±88.1
PNPH(CO)	155.6±13.9	86.6±7.4	82.8±10.3	457.0±45.0
PCO_2 (mmHg)				
LR	28.7±6.1	27.2±3.4	28.0±5.2	35.0±9.5
PNPH(CO)	29.2±4.5	26.2±3.0	29.1±6.3	38.8±11.7
BE (mmol/L)				
LR	-3.3±2.3	-8.9±2.2	-6.6±1.3	-6.3±2.8
PNPH(CO)	-3.8±3.1	-8.3±3.0	-4.0±3.3	-3.8±3.2
Lactate (mmol/L)				
LR			2.1±0.7	1.1±0.4
PNPH(CO)			1.1±0.4$	1.0±0.8
Hct# (%)				
LR			17.0±2.0	27.4±3.7
PNPH(CO)			16.4±0.9	24.4±1.1
Total Hb* (g/dl)				
LR	14.6±0.4	10.4±1.3	6.7±1.3	10.5±1.3
PNPH(CO)	14.3±0.4	9.7±0.5	6.9±0.6	10.0±0.6

No evidence for adverse systemic effects of PNPH

Pre-hospital PNPH benefit may not be mediated by an increase in Hb—although the delta from end of shock trends greater for PNPH

In vitro models of neuronal injury relevant to TBI: Effect of PNPH

Lina Du, PhD

Exposure of cortical neurons in culture to PNPH vs control Hbs

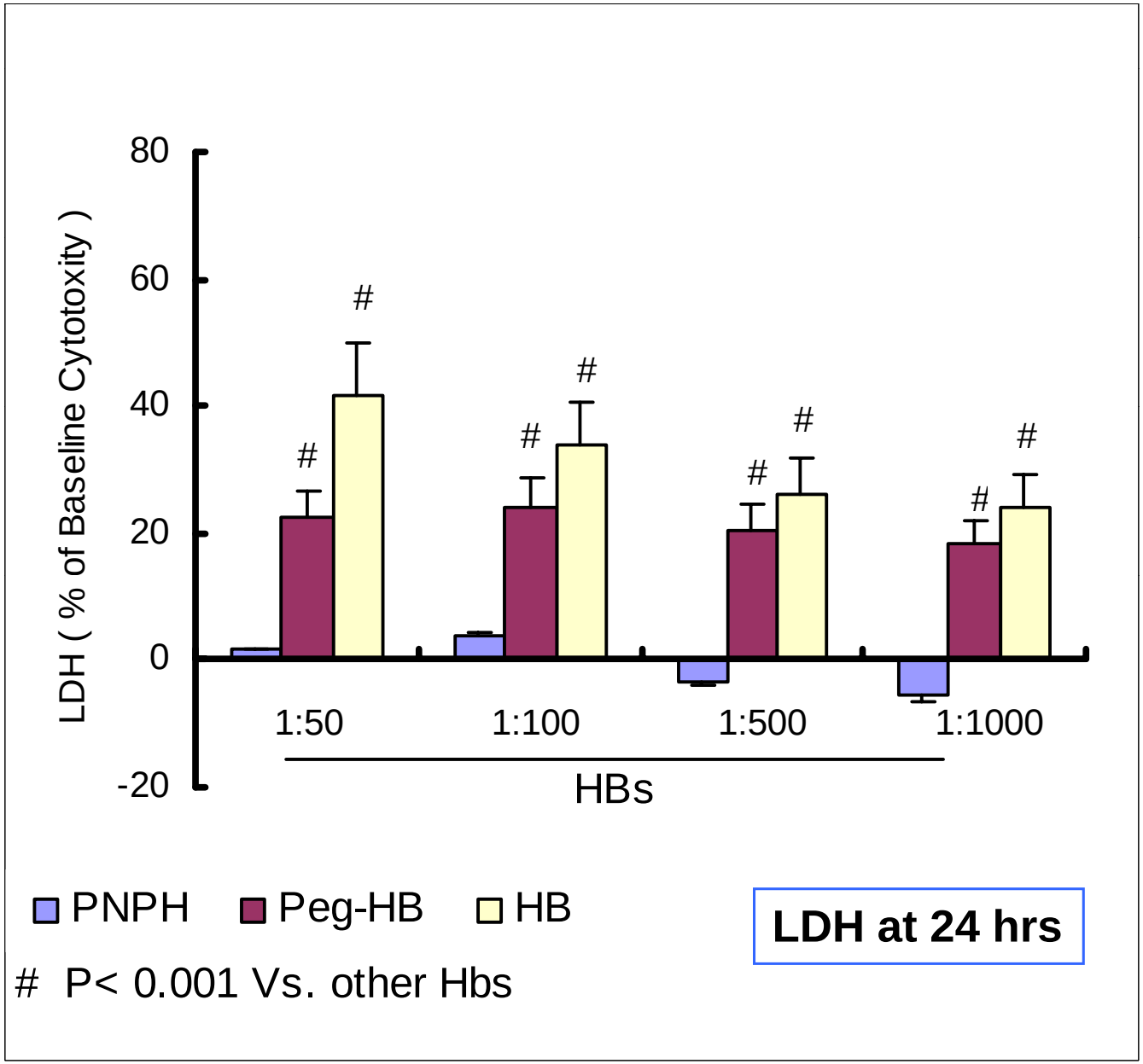
In TBI, one concern is what the consequences might be of PNPH (or any HBOC for that mater) extravasation into injured brain—given that Hb is neurotoxic

Glutamate/glycine: Excitotoxicity is a well-recognized patho-mechanism in clinical TBI

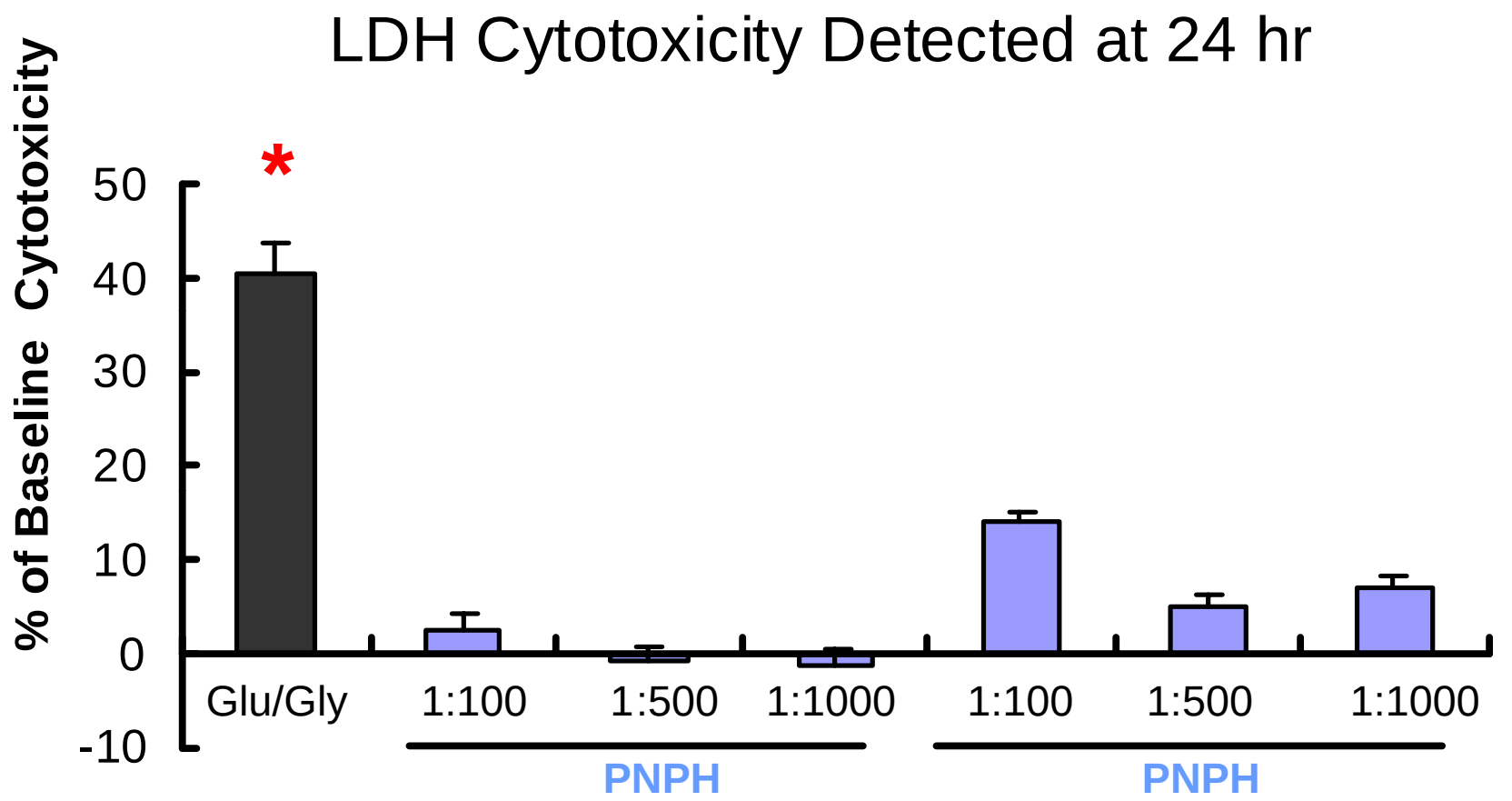
Neurotoxicity of Hb
EC50 for neuronal death in cell culture is 1-2.5 μM
Regan and Panter, Neurosci Lett, 1993

Neuronal stretch: An established and well-characterized model of *in vitro* TBI

PNPH is not toxic to neurons in culture across a wide concentration range

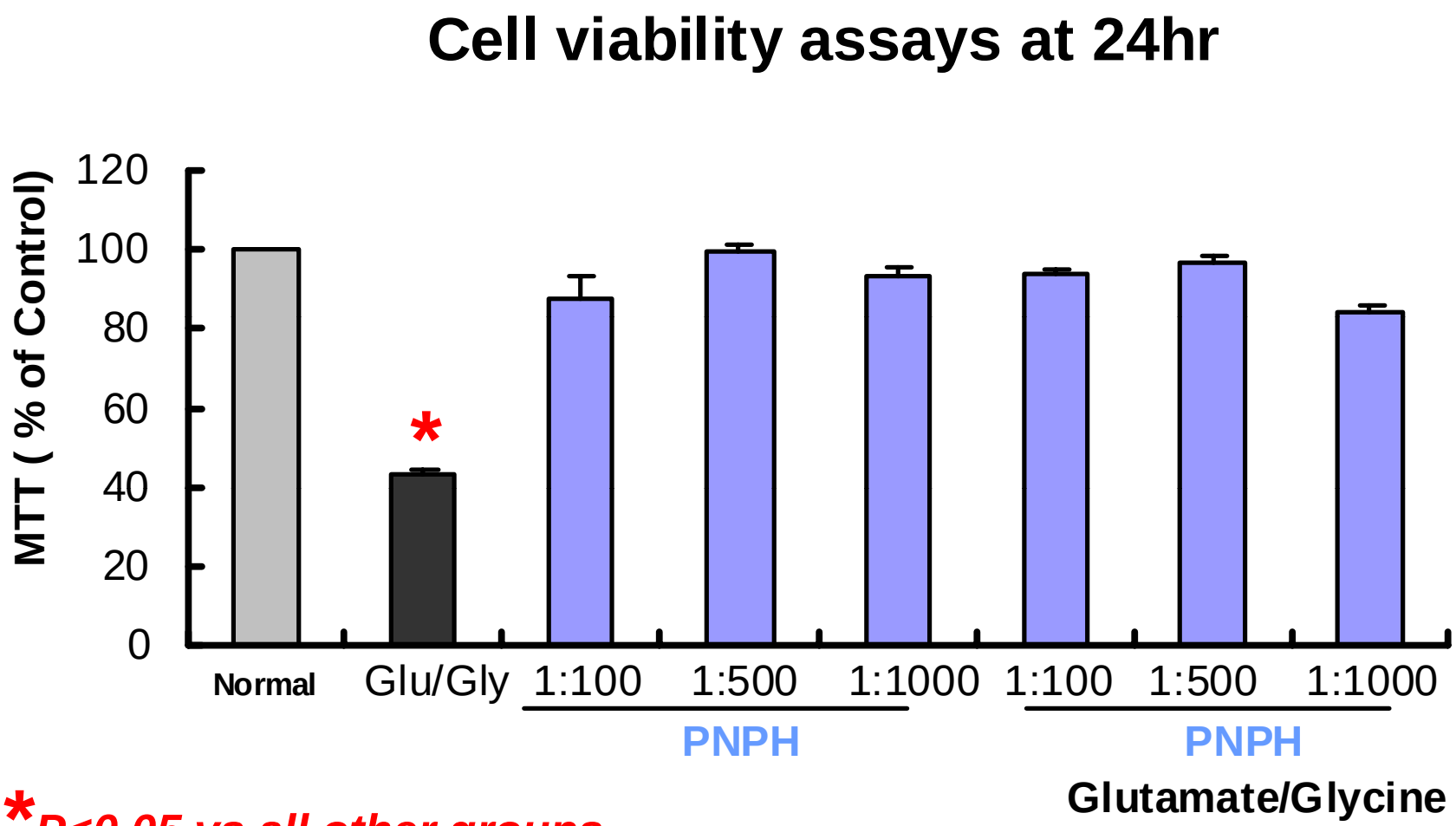


PNPH is neuroprotective in neuronal culture: Glutamate/glycine toxicity, LDH release



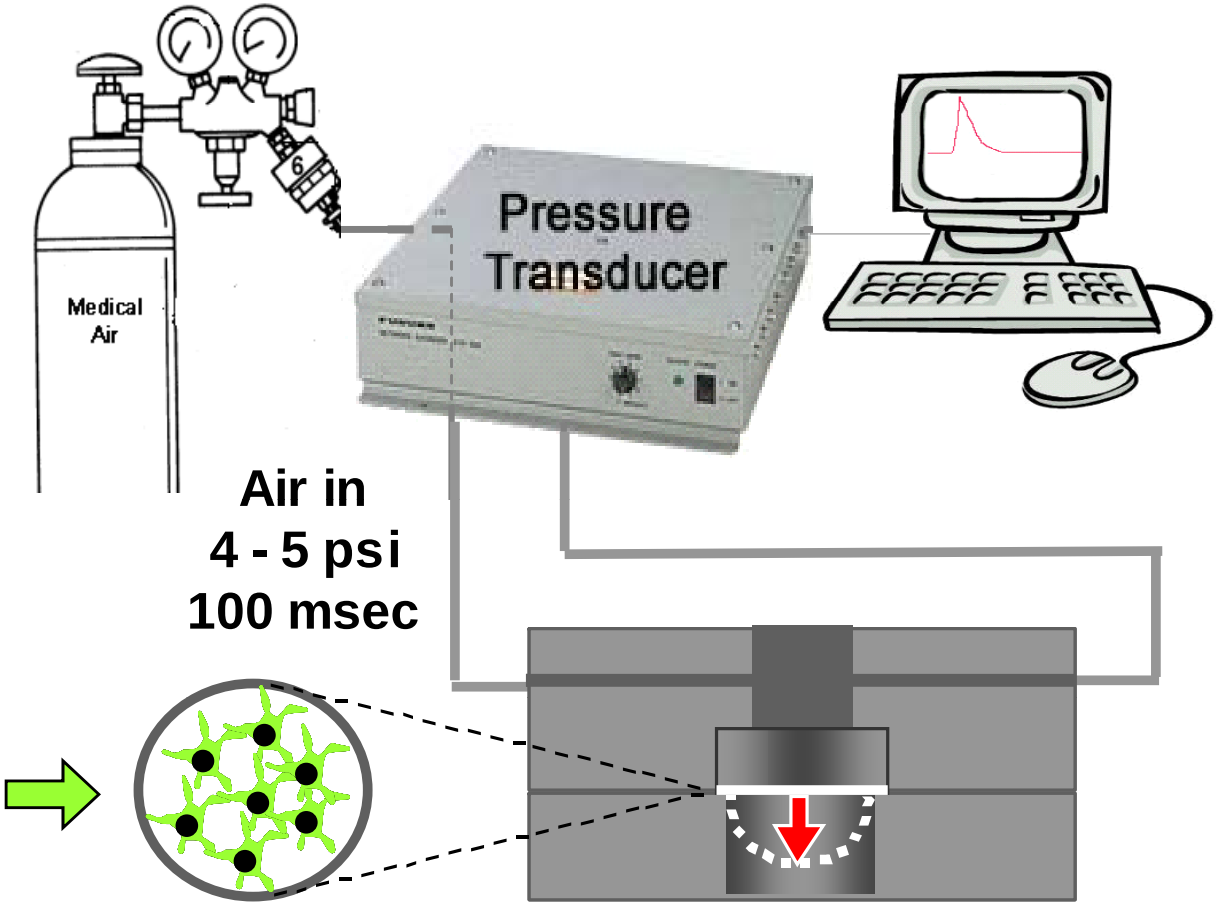
*P<0.05 vs all other groups

PNPH is neuroprotective in neuronal culture: Glutamate/glycine toxicity, MTT



*P<0.05 vs all other groups

In vitro TBI: Neuronal stretch model



Hülya Bayır, MD

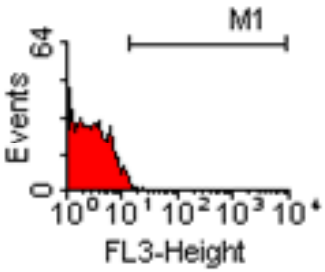
Robert Clark, MD

Primary neurons cultured on a clear silicone membrane

David Meaney

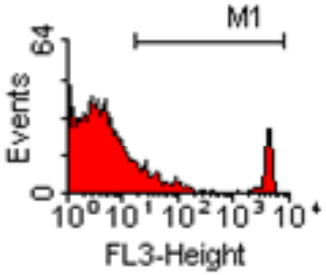
Preliminary studies of *in vitro* TBI: Neuronal stretch
Flow cytometric analysis-PI labeling
PNPH is neuroprotective

Control



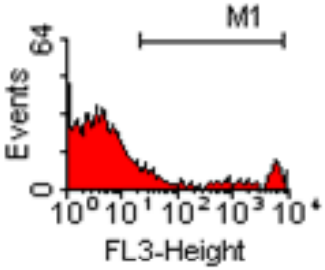
PI 3.59 %

Stretched -24hr



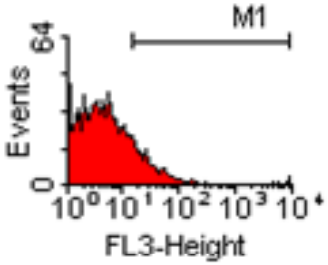
PI 22.24 %

HB- Stretched-24hr



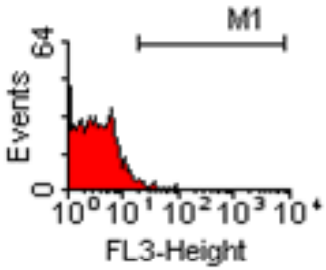
PI 29.89 %

Peg-HB-Stretched 24hr



PI 17.57 %

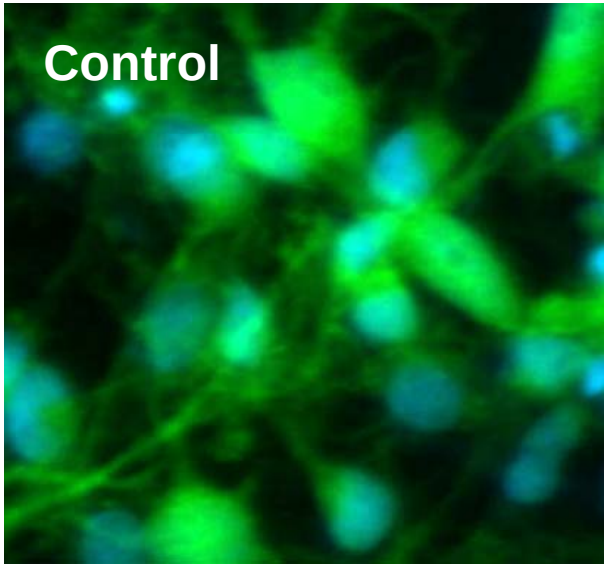
PNPH-Stretched -24hr

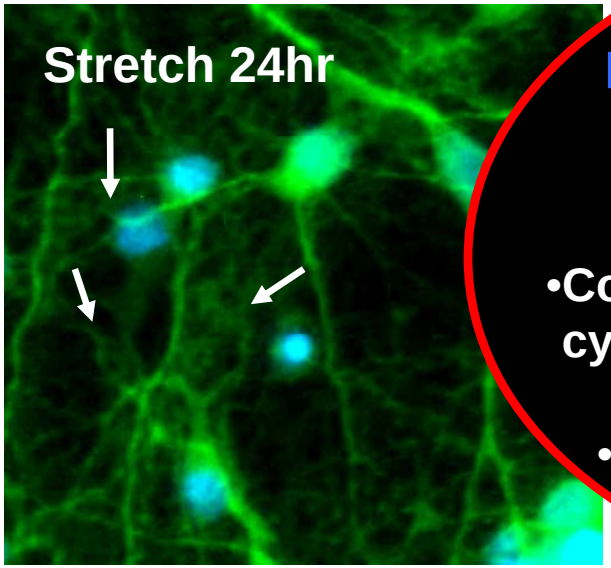


PI 7.49 %

Effect of various Hbs on morphology of cortical neurons 24 h after stretch

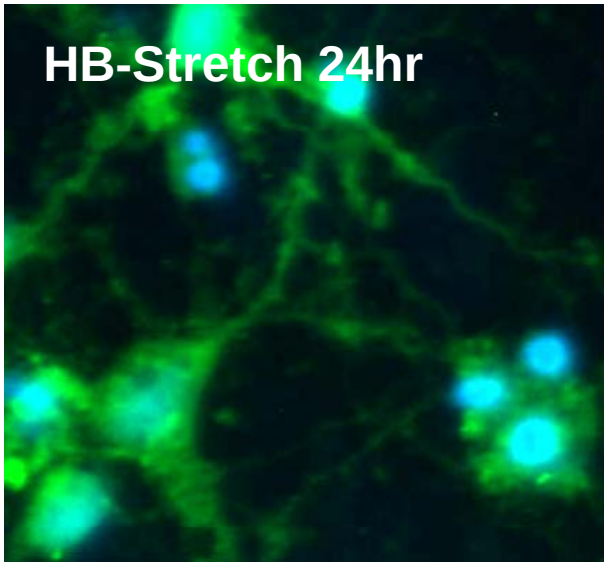
(Map 2 immunoflurescent staining)

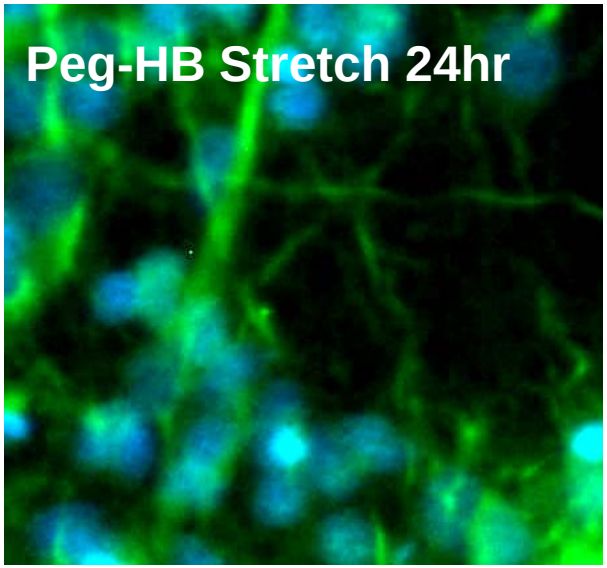


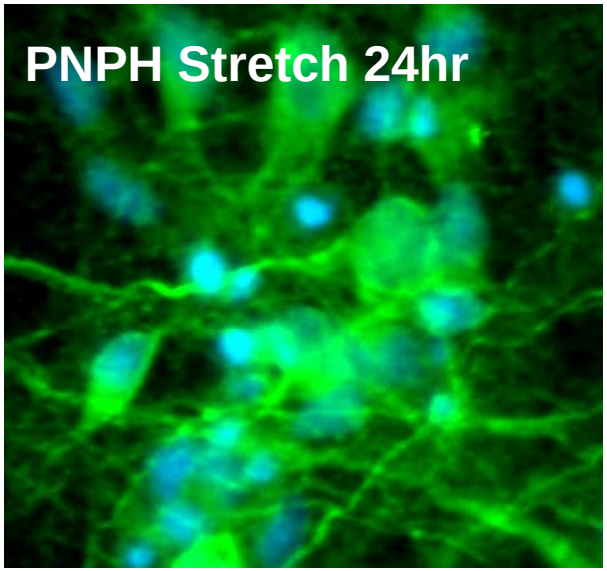


PNPH: A neuroprotective rather than neurotoxic Hb

- An exciting new agent
- Covalent modification of Hbs with cytoprotective moieties deserves exploration
- Cytoprotection outside CNS?







Some of the current funded TBI projects at the Safar Center:

- Therapeutic hypothermia bench to bedside
- Novel TBI resuscitation
- Autophagy in TBI
- Oxidative & nitrative stress and oxidative lipidomics in CNS injury
- Adenosine and cAMP in TBI
- Calcineurin in TBI
- Dopamine signaling in TBI therapy and rehabilitation
- Enriched environment in TBI recovery
- Biomarkers in child abuse and pediatric neurointensive care
- CBF promotion in cerebral resuscitation after cardiac arrest
- Extracorporeal resuscitation after cardiac arrest
- Emergency preservation and resuscitation
- P-glycoprotein transporters in TBI therapy
- Novel findings in blast TBI
- Drug screening for blast TBI and polytrauma

DARPA

PREVENT
Preventing Violent Explosive Neurologic Trauma

Other components

Walter Reed Army Institute of Research

Harvard University

ORA

Yale University

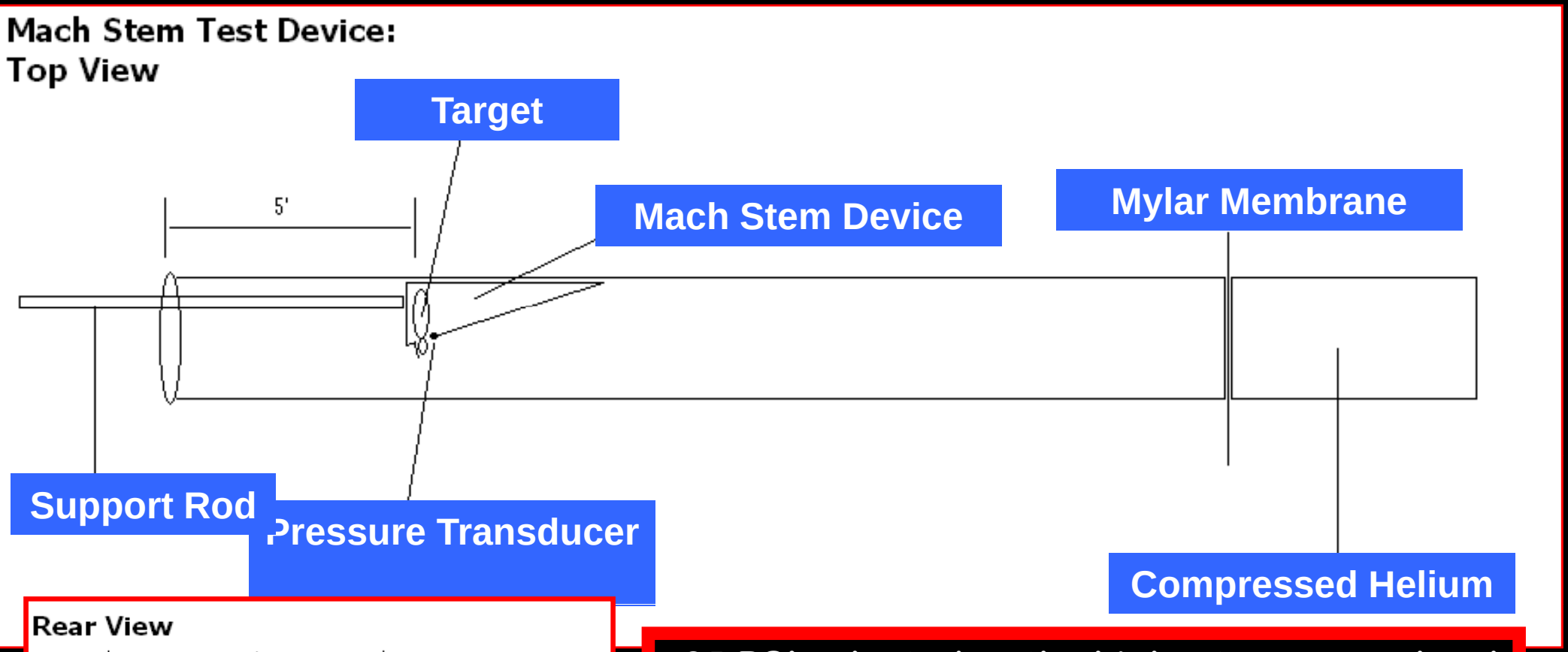
Safar Center

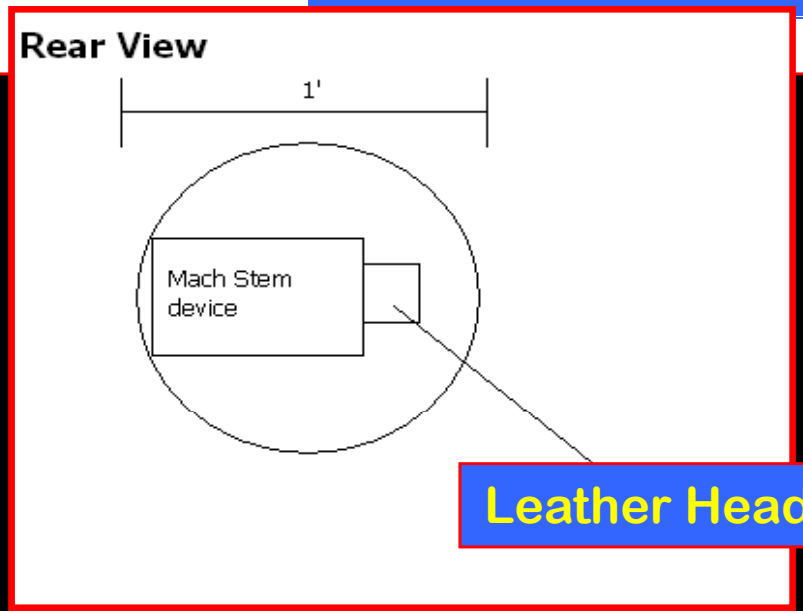
Uniform Services University of the Health Sciences

Characterize the neuropathological, molecular, cellular, and biochemical signature of blast-induced TBI in rodents

Characterize an explosion blast TBI model in pigs

Rat model of blast TBI: PREVENT Program





- 35 PSI selected as the highest exposure level that the rats could consistently survive
- Survival was ~75% --death resulted from immediate or early post insult apnea (within 1 min of blast exposure)

Typical Blast Tube (25 ft)

to produce rodent Traumatic Brain Injury

PREVENT
Preventing Violent Explosive Neurologic Trauma

Recovery of Righting reflex

- 35 PSI Blast-TBI –546 ± 51 sec (~9 min 06 sec)
- **CCI (~7 min; moderate CCI; 4 m/s, 2.8 mm depth [Wagner et al, 2005])**
- **FPI (6.5 min; standard FPI; 2 ATM [Whiting and Hamm, 2008])**

- **Somewhat high mortality rate for this duration of RR; and given that this represents blast injury with isolated head exposure**

- **Many extremely interesting an unique findings**

24 hours

Cerebellum

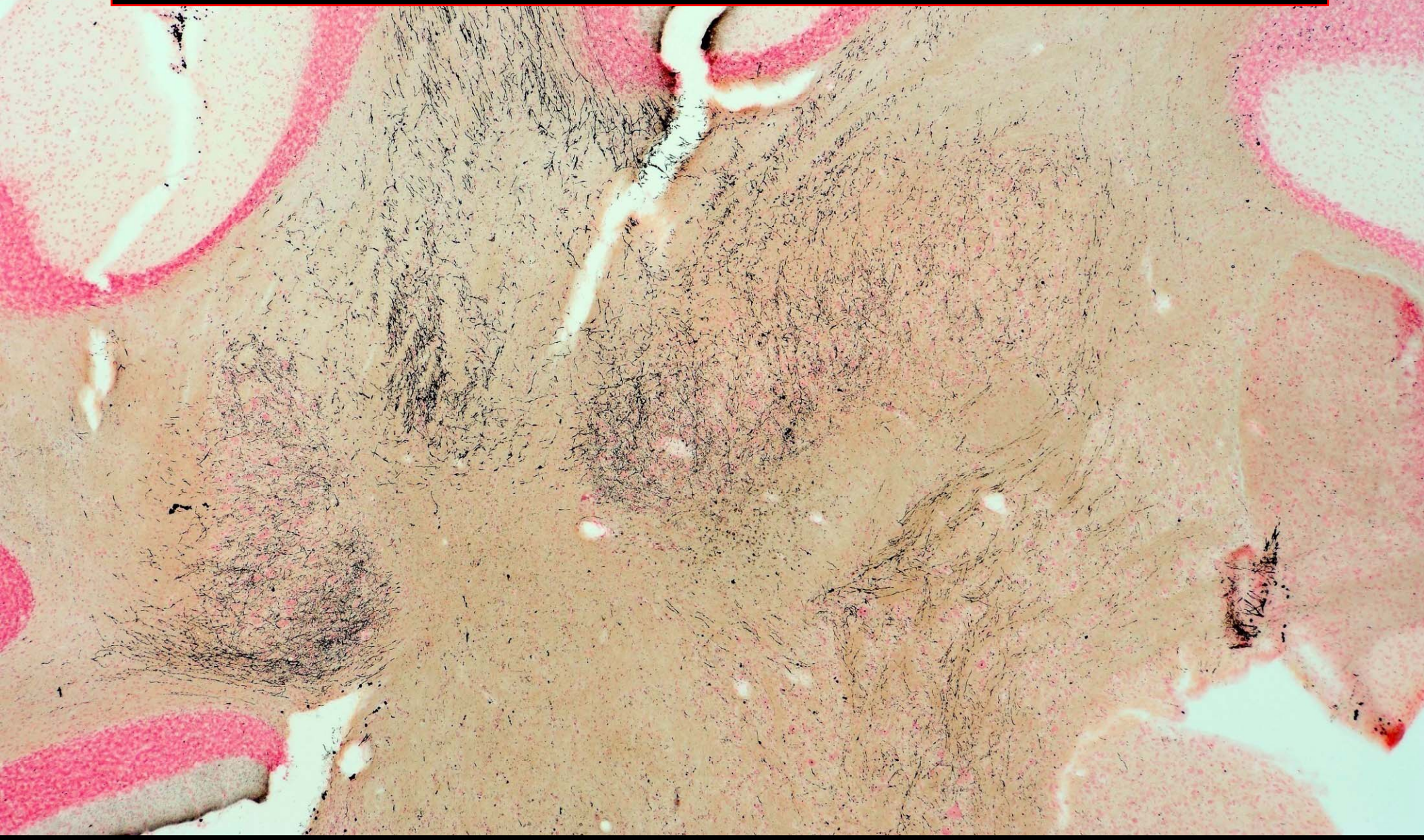
- Degeneration of purkinje dendrites in molecular layer
- Axonal injury in the granular layer
- A few dead purkinje neurons

24 hours

24 hours

Cerebellum

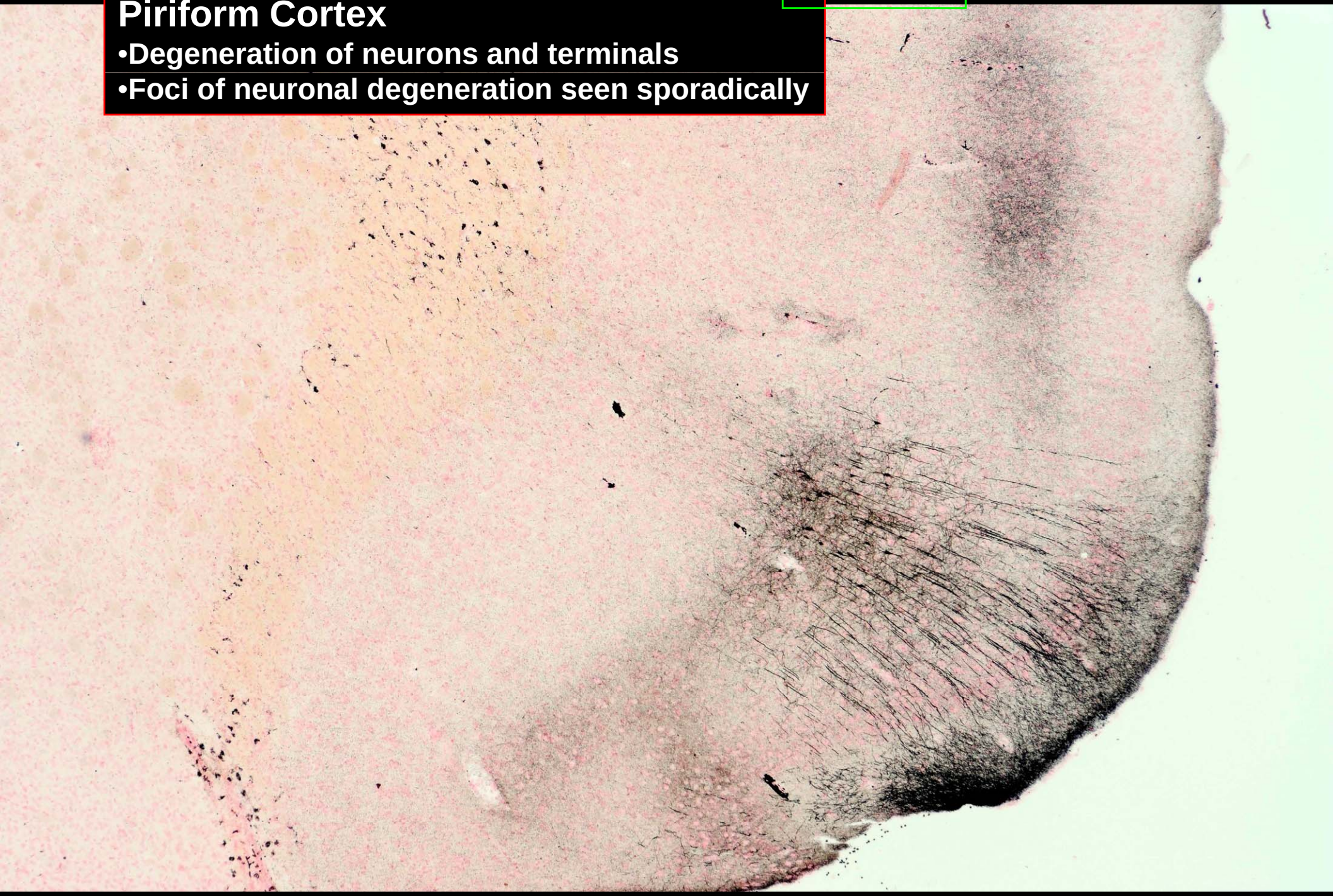
- Widespread axonal injury in white matter— in every animal at every time point
- Slightly greater damage contra-coup—blast is a global insult



24 hours

Piriform Cortex

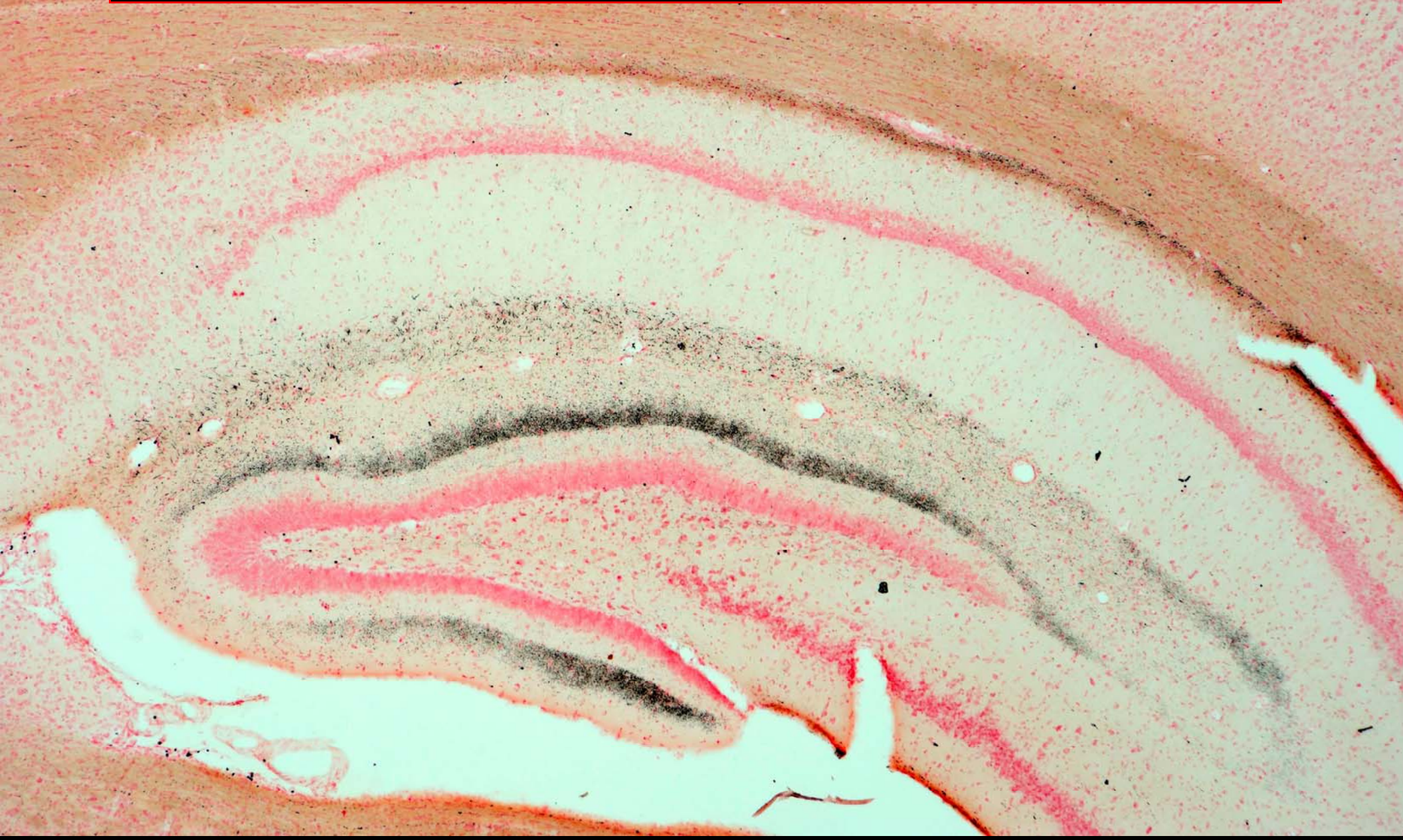
- Degeneration of neurons and terminals
- Foci of neuronal degeneration seen sporadically

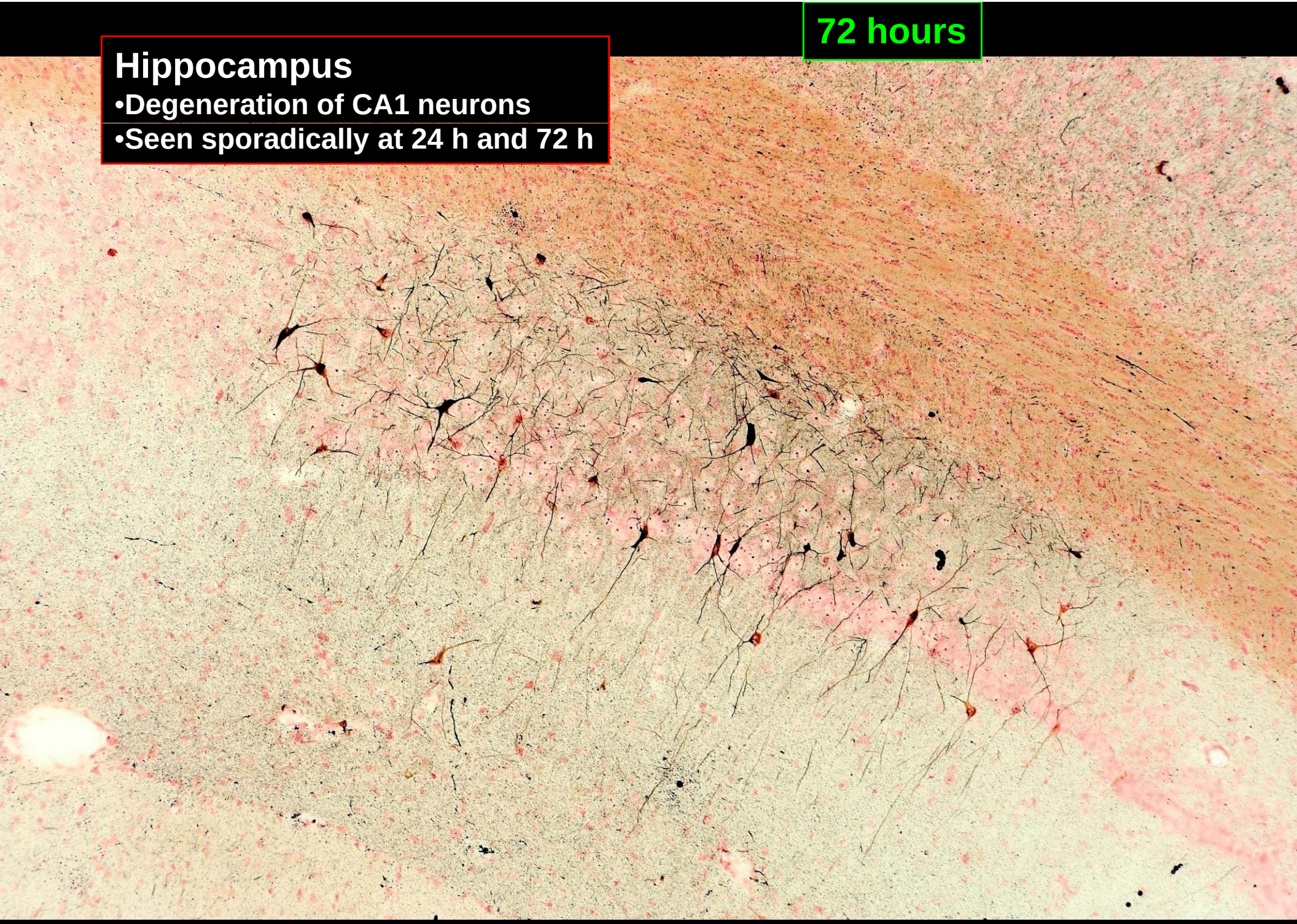


Hippocampus

72 hours

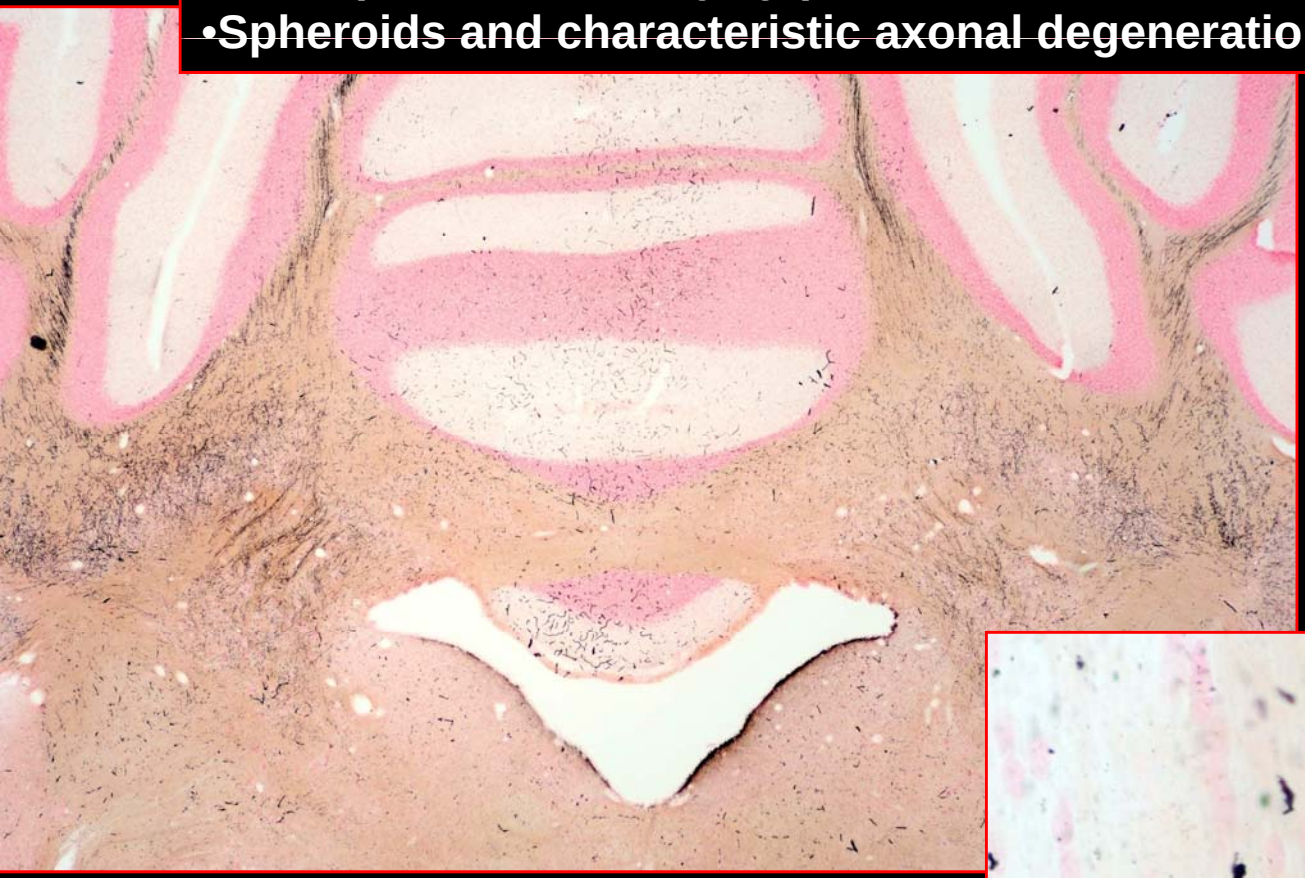
- Degeneration of perforant pathway axons and dentate granule cell dendrites
- Seen in every animal at 24 and 72 hrs —gone at 2 weeks



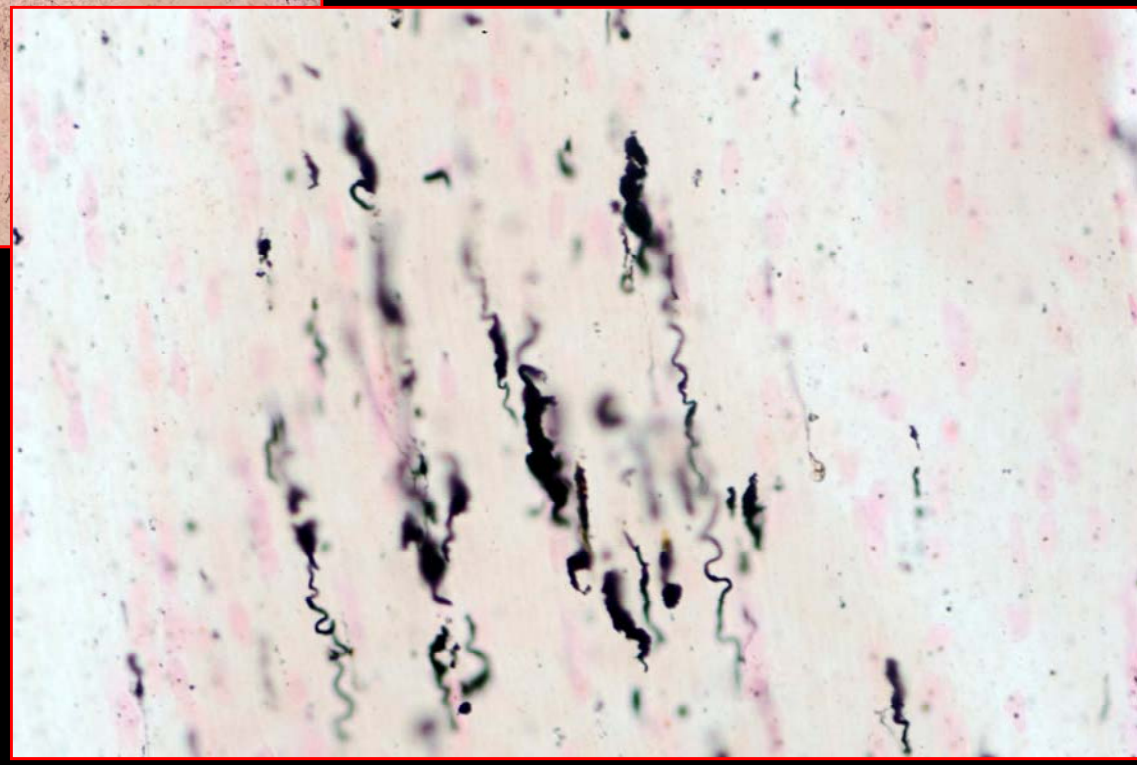

72 hours
Hippocampus
•Degeneration of CA1 neurons
•Seen sporadically at 24 h and 72 h

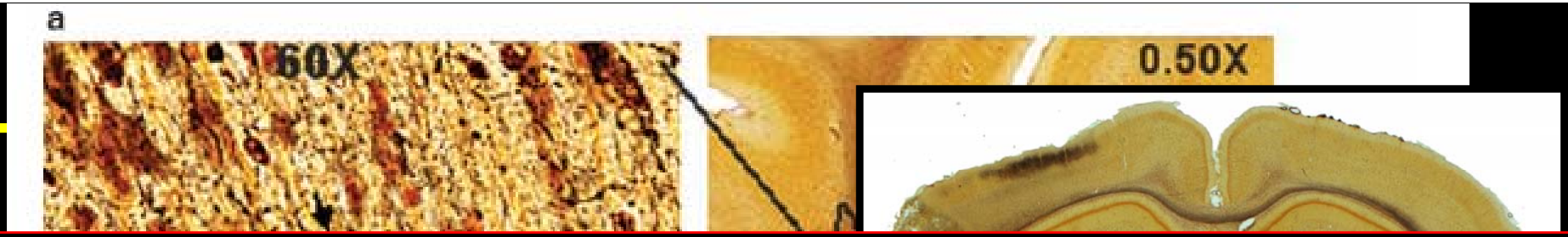
Cerebellum

- Widespread axonal injury persists in white matter at 72 hours
- Spheroids and characteristic axonal degeneration profiles at higher magnification



2 Weeks





H n

Conclusions DARPA PREVENT Phase I:

1. **Rodents and an air blast overpressure insult can be used to effectively model important elements of explosive blast TBI**

2. **Axonal injury and terminal degeneration appear to be key features—out of proportion to neuronal death vs other conventional models**

3. **Current studies in our laboratory are characterizing the molecular, cellular, and biochemical changes and evaluating therapies**

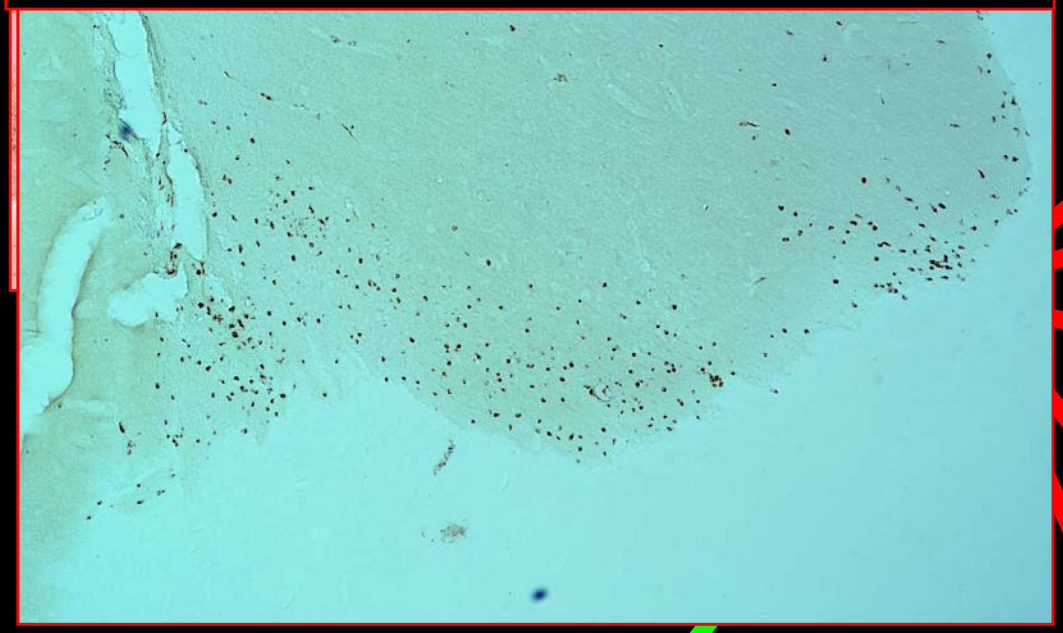
4. **Fiber track and axonal damage—may be key therapeutic and biomarker targets for blast TBI**

5. **Silver staining of axonal injury and fiber track degeneration should be strongly considered as an important outcome for drug screening studies**

A

PREVENT PHASE I-II

ED-1+ macrophage accumulation at 24 h in cortex



Immunohistochemical screening
Fluoro-Jade B—neuronal death
GFAP—Astrocyte proliferation
ED-1—Macrophage response
Iba-1—Microglial response

Gene Array

Purine metabolites
adenosine, cAMP

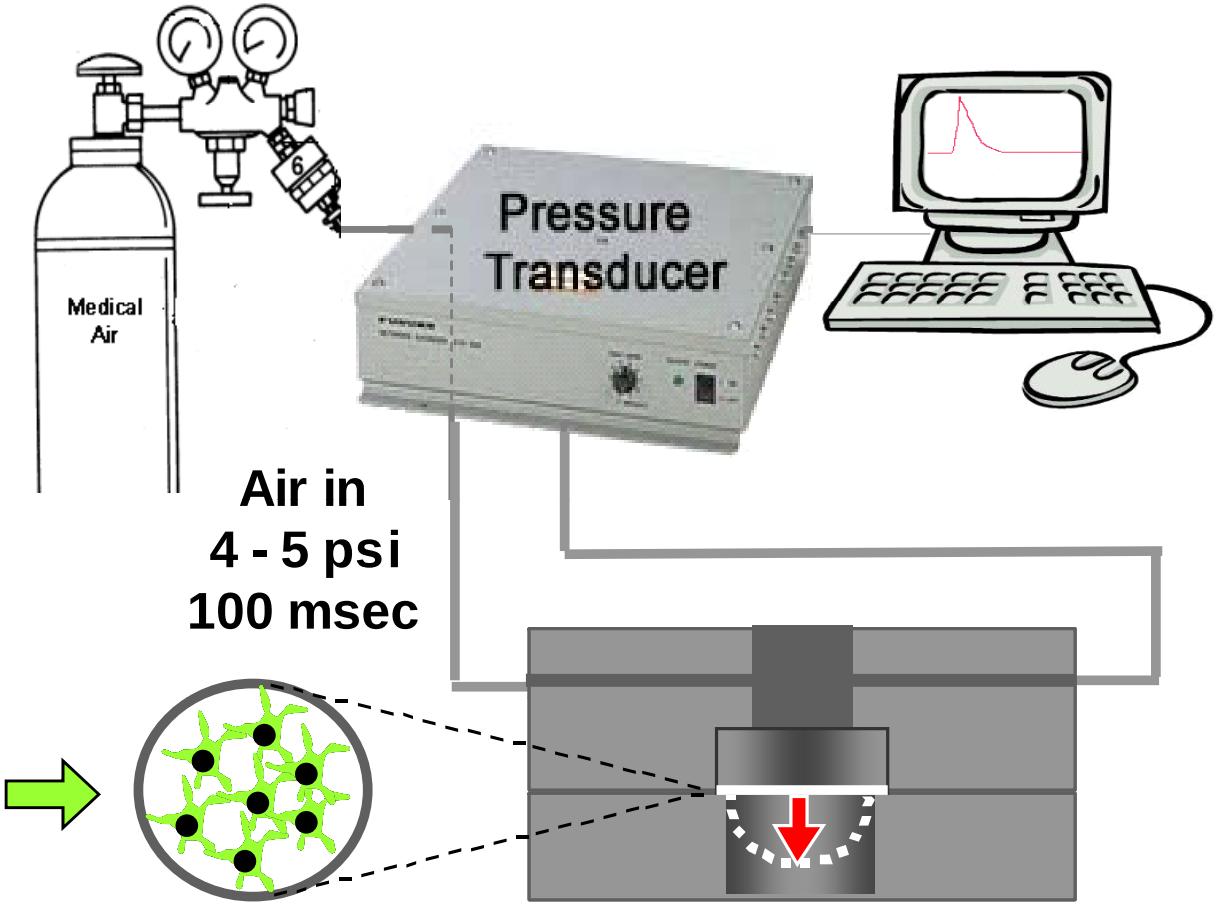
Cytokine Luminex

Battery of oxidative stress
and nitrative stress markers

Mitochondrial oxidative lipidomics

In vitro TBI: Neuronal stretch model

Essential to our NIH-funded TBI projects—since other models such as glutamate, oxygen/glucose deprivation etc are not considered TBI

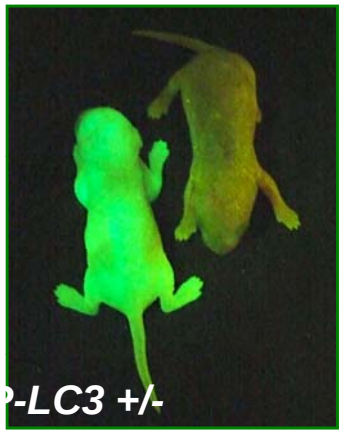


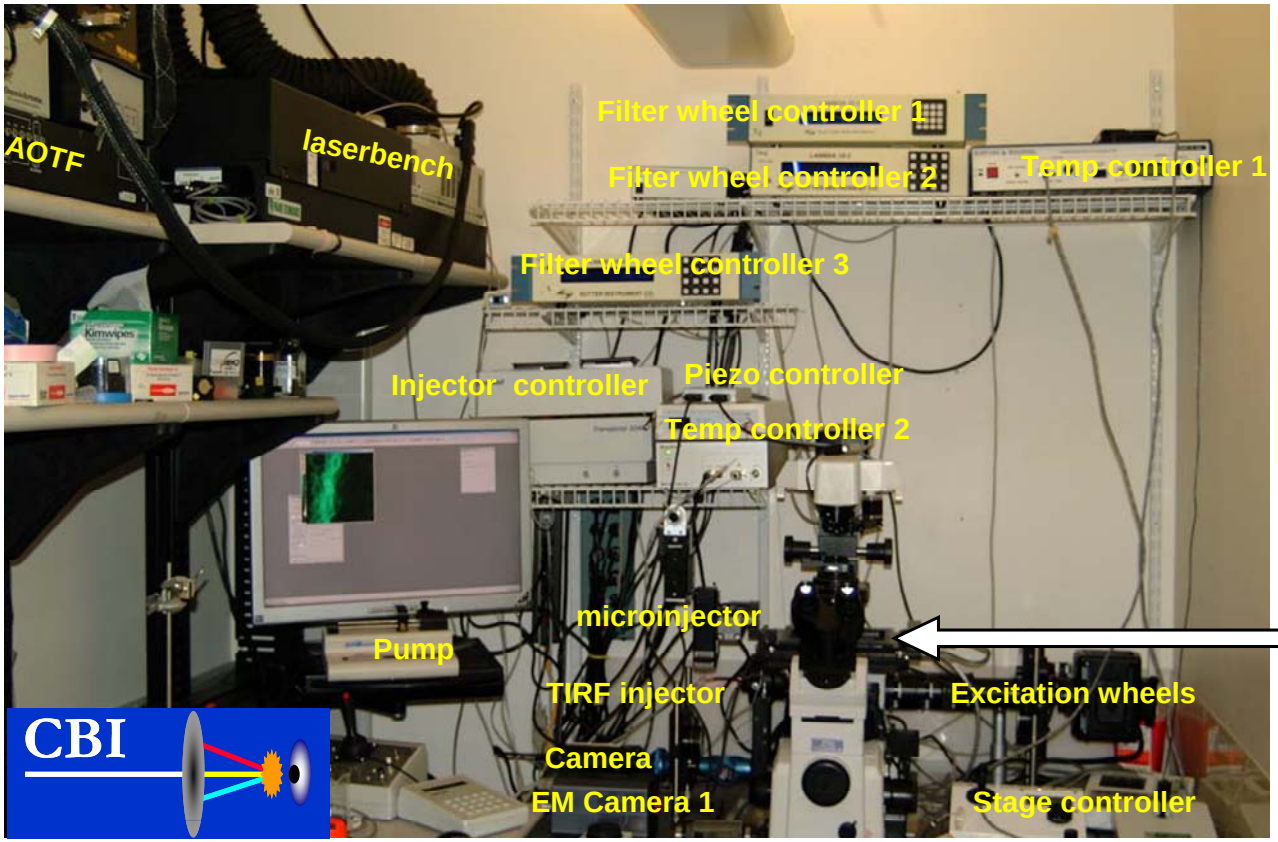
Primary neurons cultured on a clear silicone membrane

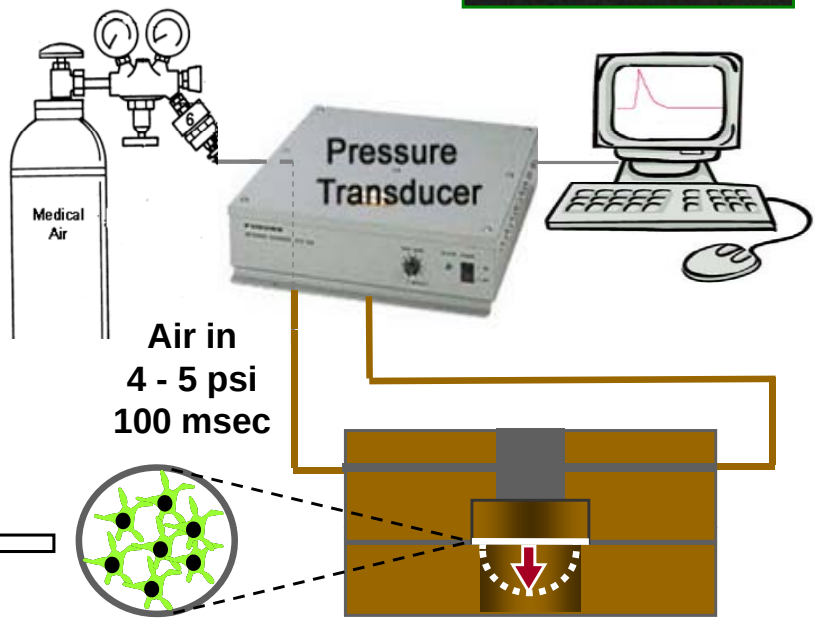
Hülya Bayır, MD

Robert Clark, MD

Live cell imaging + in vitro trauma







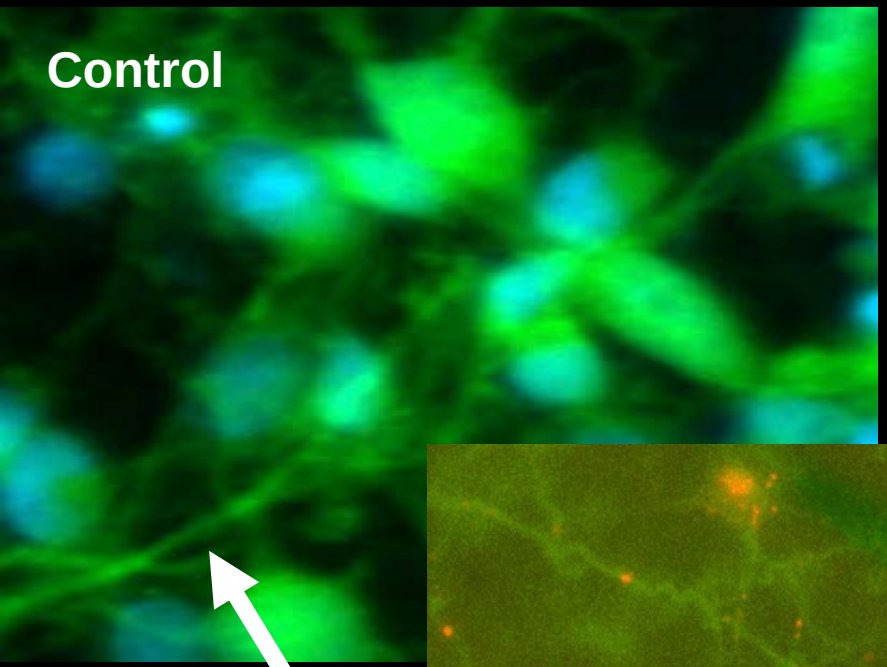
Primary neurons cultured on a clear silicone membrane

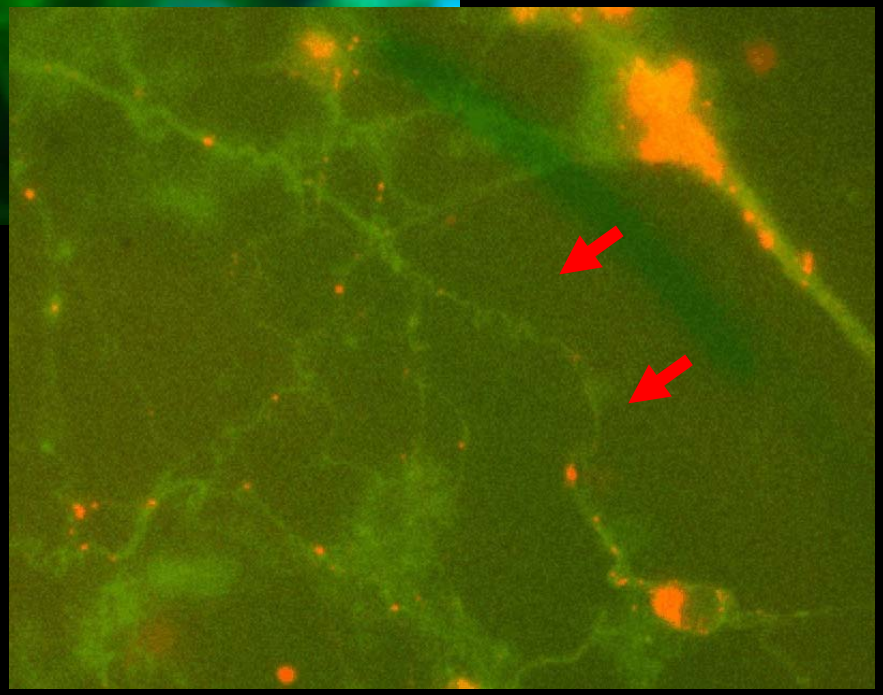
Simon Watkins, PhD

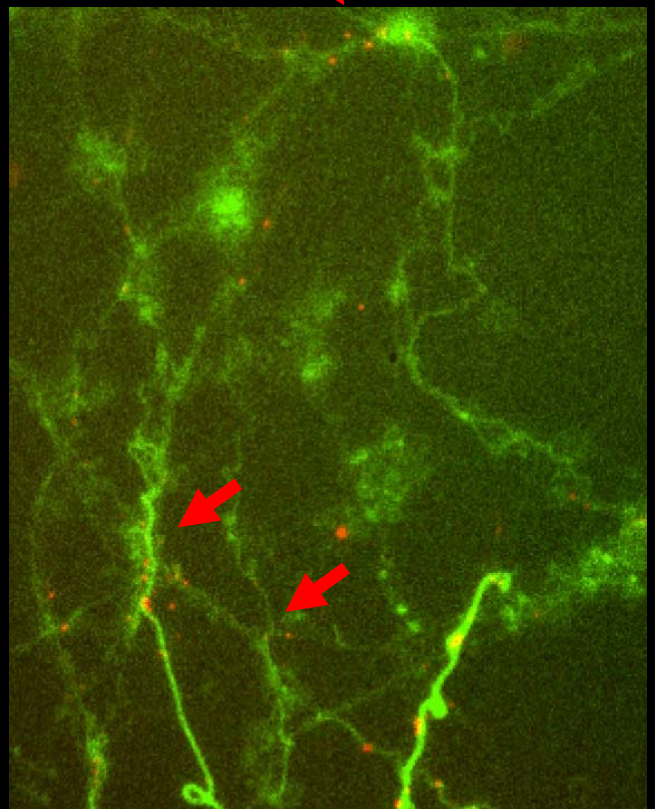
Severe neuronal damage can recover!

A potential high-throughput therapeutic screening model for fiber track damage in blast-induced TBI

Neurite *fluidity and* ***lysosome*** *trafficking after stretch-induced injury*







Time lapse over ~1 hr

LysoTracker (Molecular Probes)

Other therapies?

Low hanging fruit—FDA approved for other uses?

- Progesterone
- FK-506
- Cyclosporin-A
- Pioglitazone
- Atorvistatin
- Lovastatin
- Simvastatin
- Minocycline
- EPO
- Rolipram
- Pentostatin
- Lithium
- Deferoxamine
- Nitrite

Caffeine
Sulforaphane
Huperzine A
Resveratrol

High risk high reward?

- NNZ-2566
- Hemigramicidin Tempol conjugates (XJB-5-125)
- Poloxamer-188
- Necrostatin
- Anti-ASCab
- Anti-CD11b
- PNPH

Journal of Cerebral Blood Flow & Metabolism (2008) 28, 1114–1126
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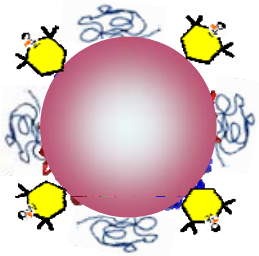
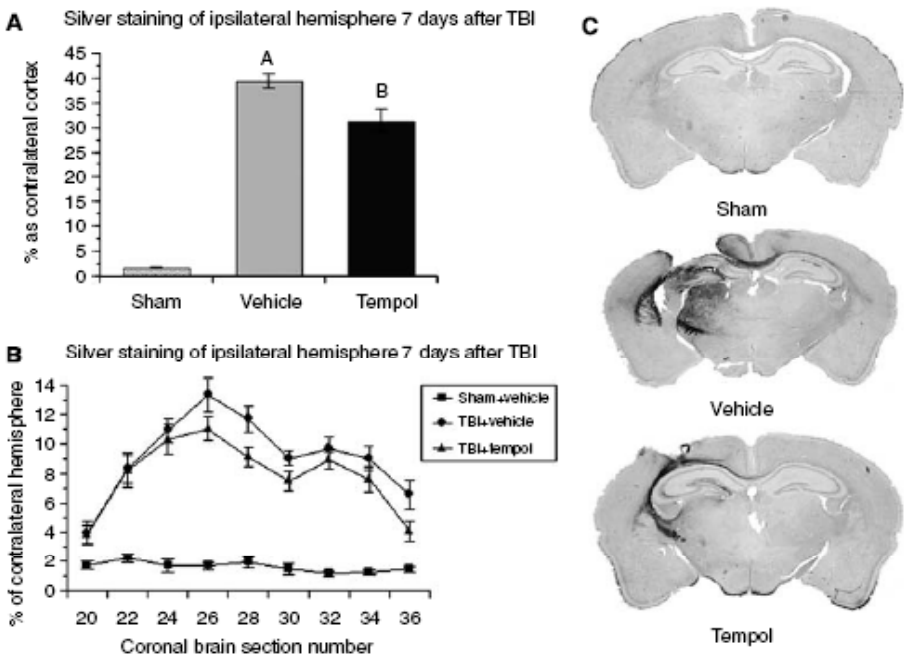
www.jcbfm.com



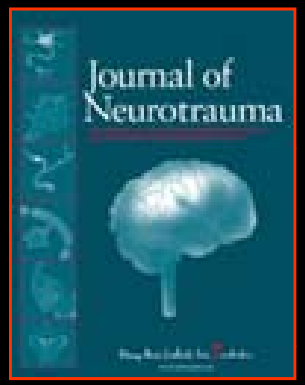
Neuroprotective effects of tempol, a catalytic scavenger of peroxynitrite-derived free radicals, in a mouse traumatic brain injury model

Ying Deng-Bryant, Indrapal N Singh, Kimberly M Carrico and Edward D Hall

Spinal Cord & Brain Injury Research Center and Department of Anatomy & Neurobiology, University of Kentucky Chandler Medical Center, Lexington, Kentucky, USA



The nitroxide tempol attenuates fiber track degeneration on silver staining after TBI in mice!



June 2009 Issue of the Journal of Neurotrauma
A special issue devoted to Blast TBI and Polytrauma

Explosive Blast Neurotrauma

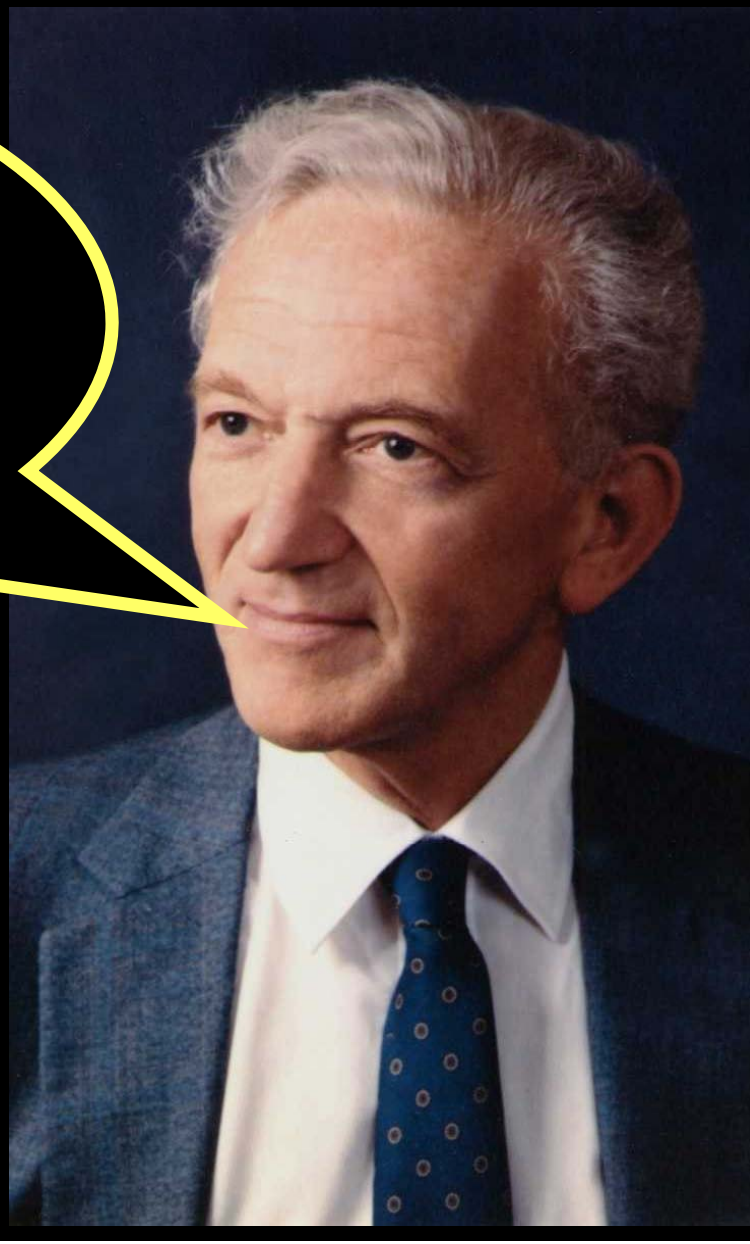
Geoffrey Ling,[1,2] Faris Bandak,[1,5] Rocco Armonda,[2] Gerald Grant,[3] and James Ecklund[2,4]

Abstract

Explosive blast traumatic brain injury (TBI) is one of the more serious wounds suffered by United States service members injured in the current conflicts in Iraq and Afghanistan. Some military medical treatments for blast TBI that have been introduced successfully in the war theater include decompressive craniectomy, cerebral angiography, transcranial Doppler, hypertonic resuscitation fluids, among others. Stateside neurosurgery, neurocritical care, and rehabilitation for these patients have similarly progressed. With experience, military physicians have been able to clinically describe blast TBI across the entire severity spectrum. One important clinical finding

The Late Peter Safar, MD

It is our duty as clinician-scientist to search for BREAKTHROUGHS— not for *p*-values



Thanks!

Support

US Army PRMRP

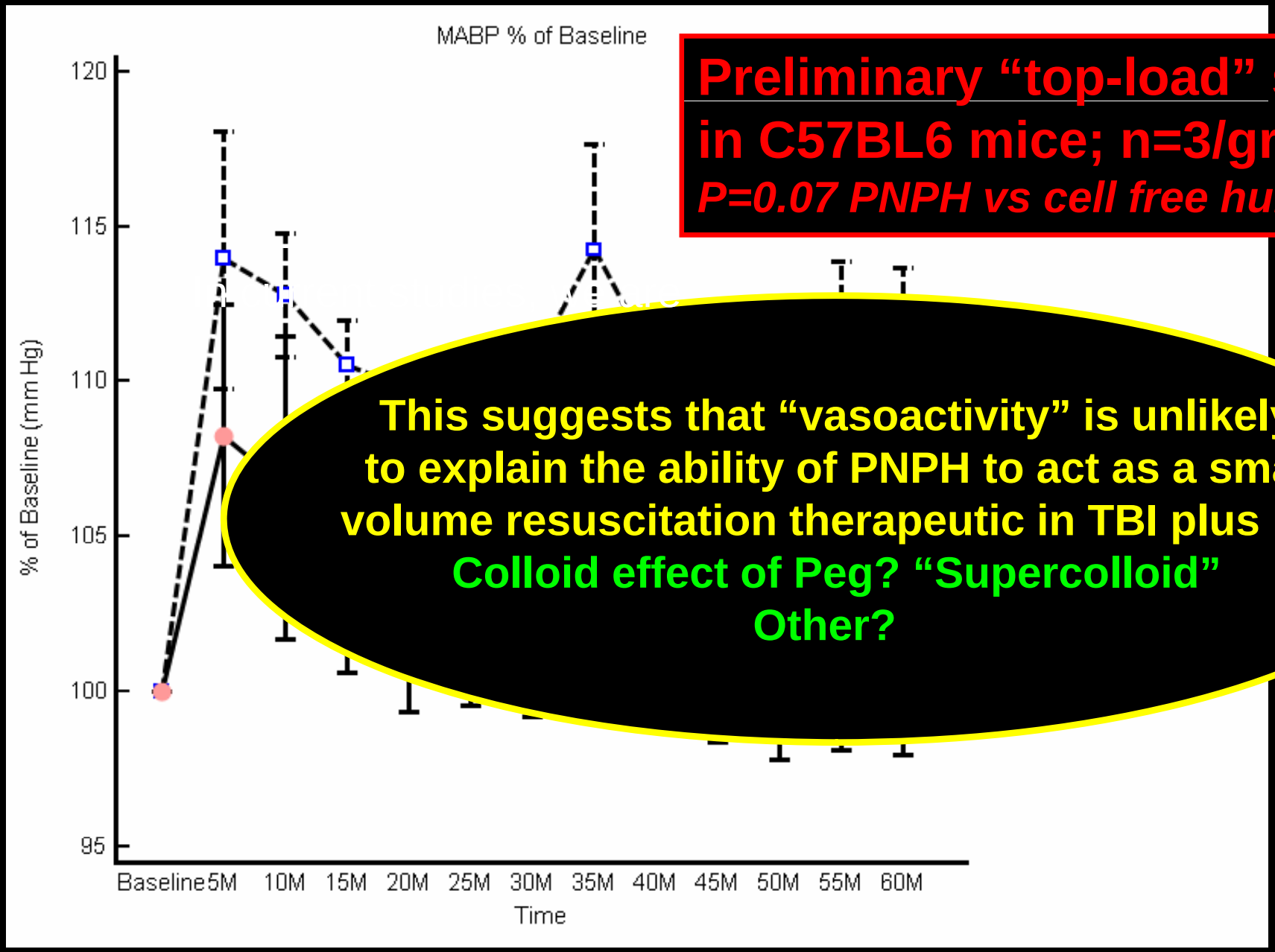
PR054755

W81XWH-06-1-0247

DARPA

PREVENT

Ongoing studies with PNPH: What about possible NO scavenging by PNPH —is it any better than cell free Hb?



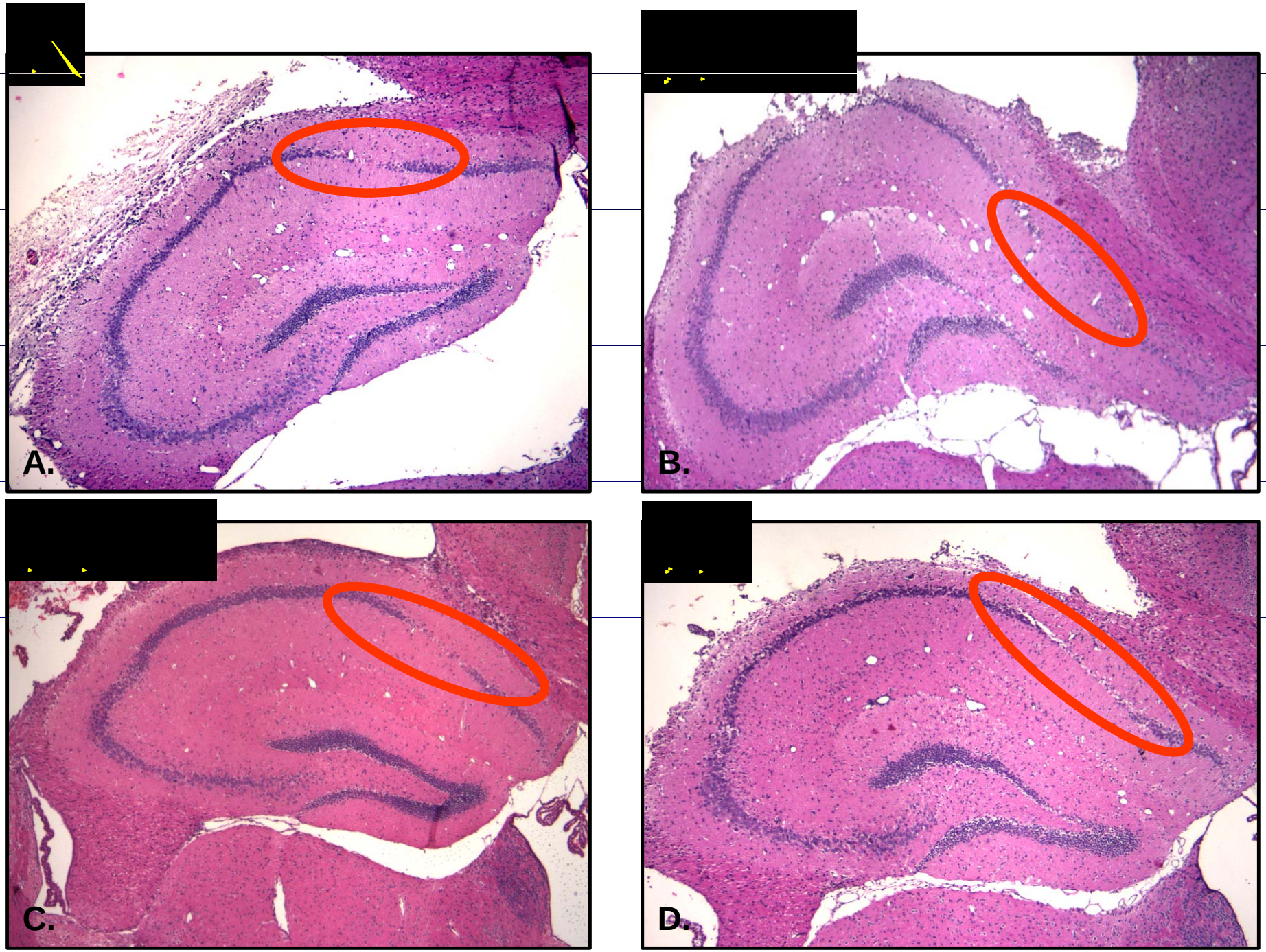
Preliminary "top-load" study in C57BL6 mice; n=3/group

P=0.07 PNPH vs cell free human Hb

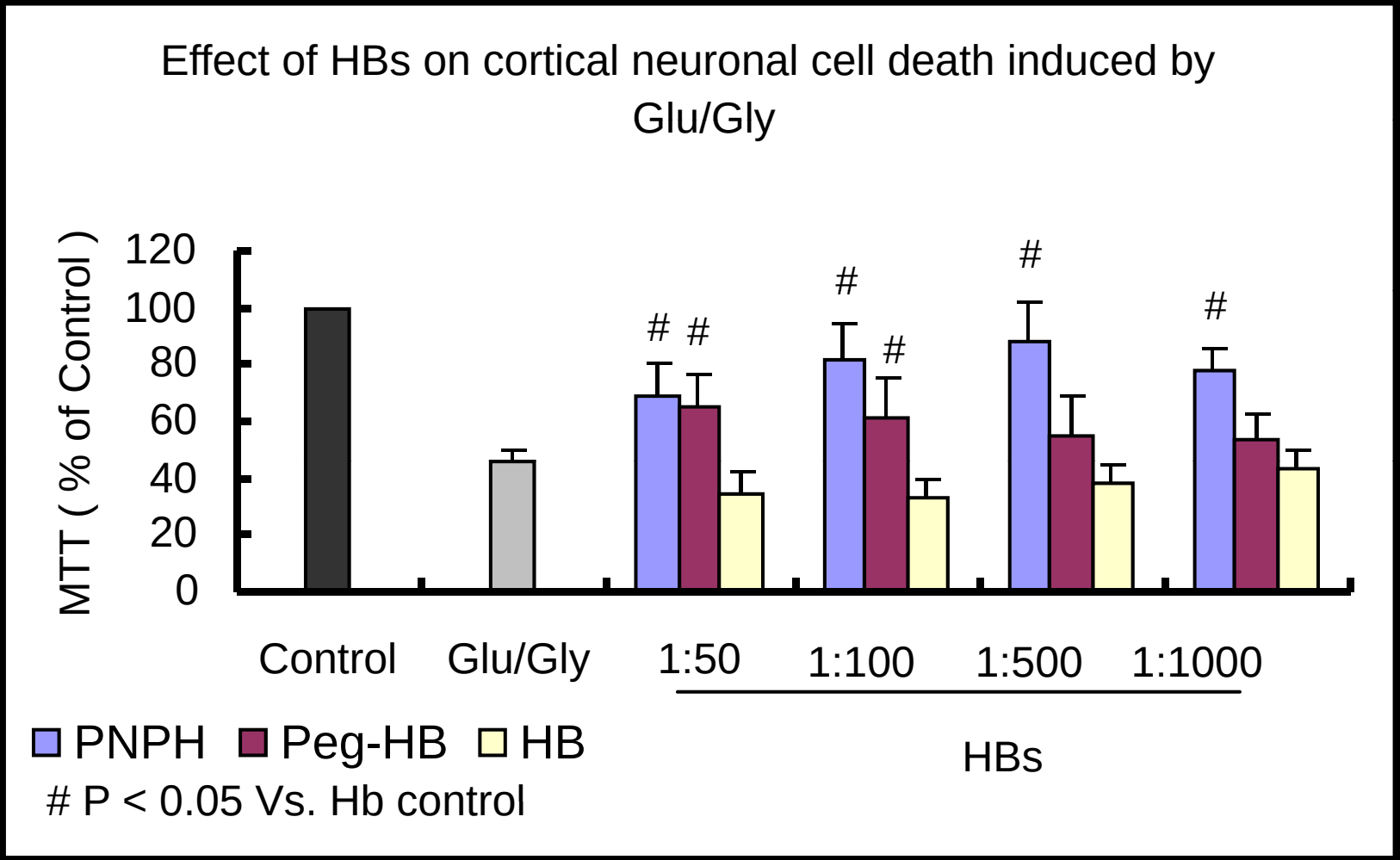
This suggests that "vasoactivity" is unlikely to explain the ability of PNPH to act as a small volume resuscitation therapeutic in TBI plus HS

Colloid effect of Peg? "Supercolloid"

Other?


A.
B.
C.
D.

Effect of Hbs on Excitotoxic Neuronal Death in Culture



Study 2

PNPH

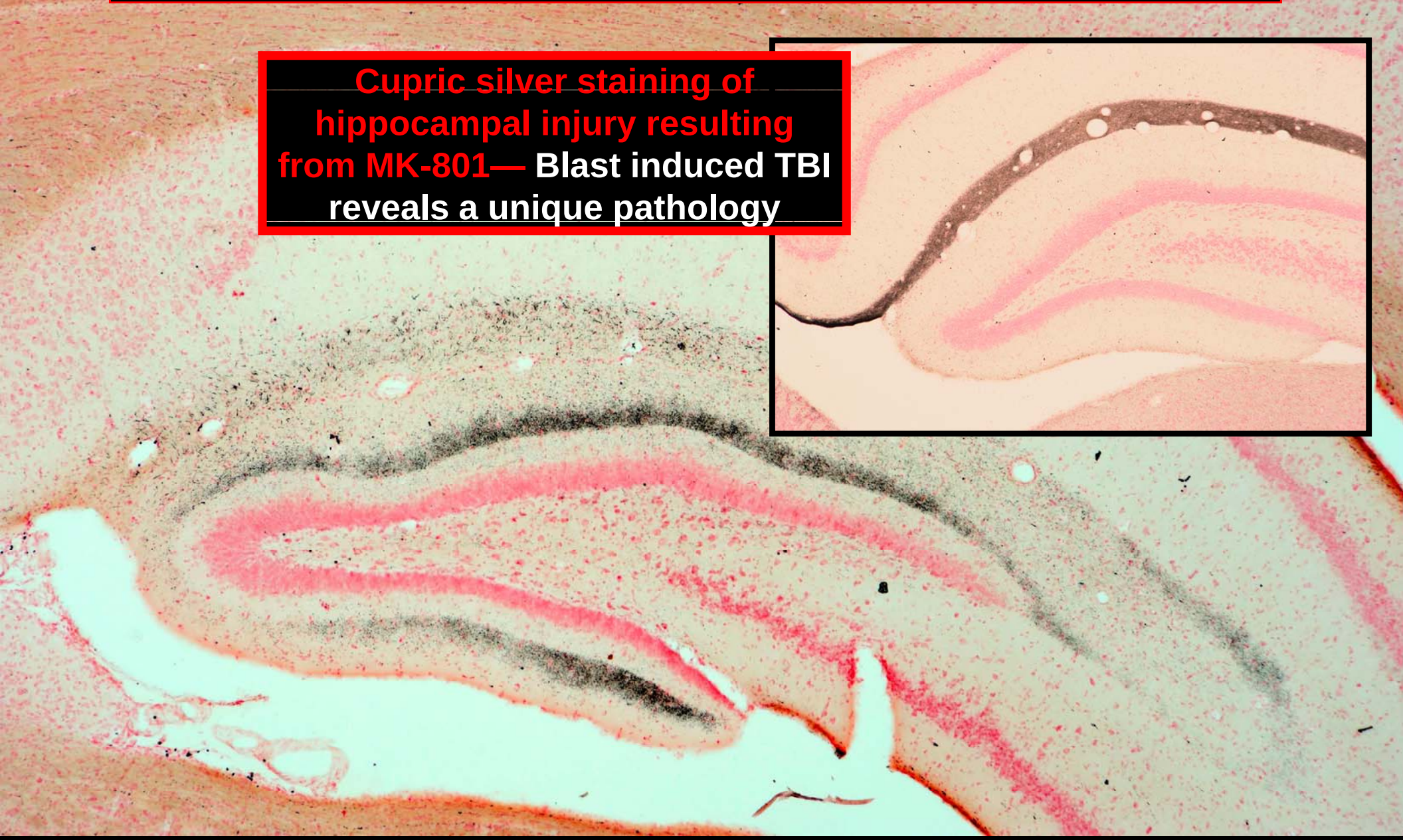
Top loading in mice

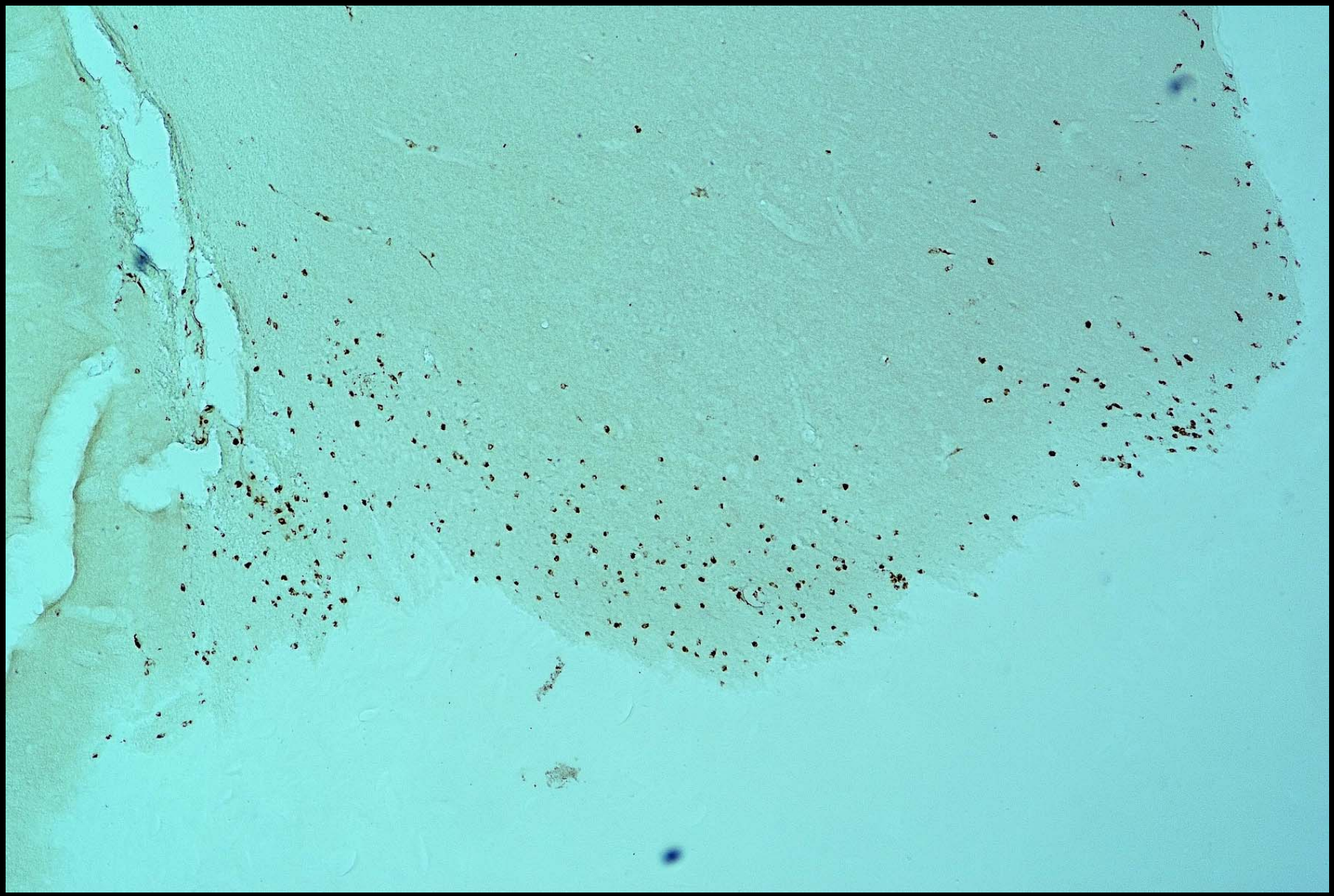
Hippocampus

72 hours

- Degeneration of perforant pathway axons and dentate granule cell dendrites
- Seen in every animal at 24 and 72 hrs —gone at 2 weeks

Cupric silver staining of hippocampal injury resulting from MK-801— Blast induced TBI reveals a unique pathology

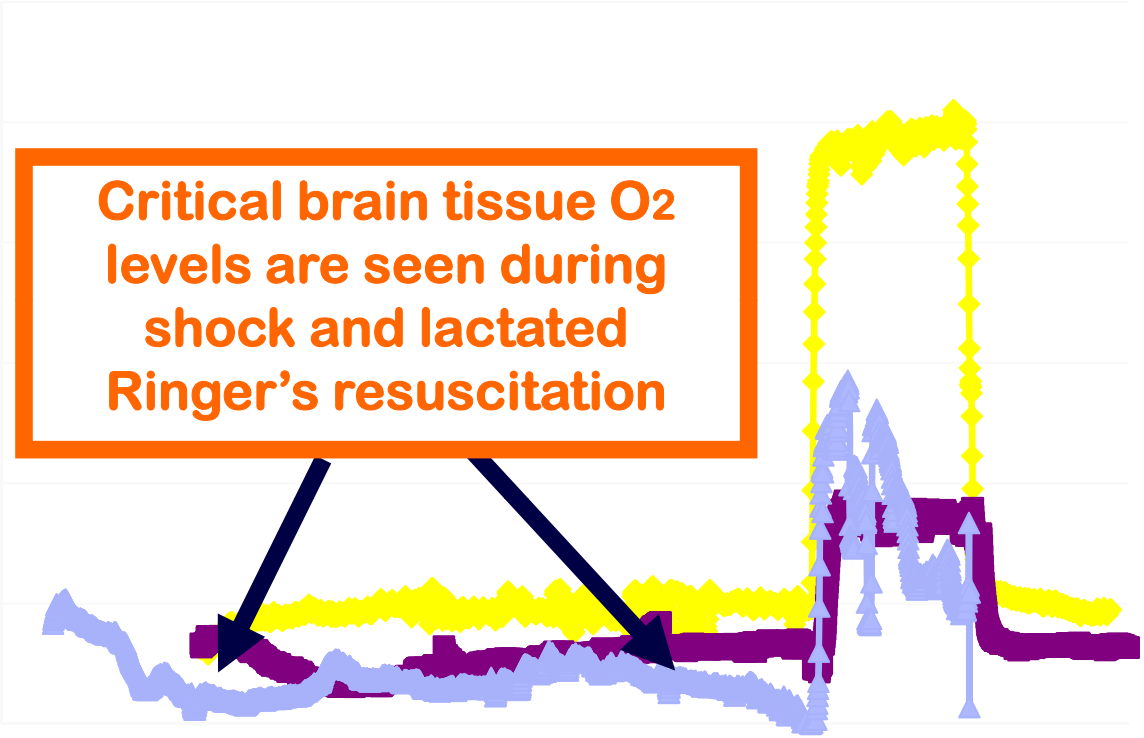




24 H

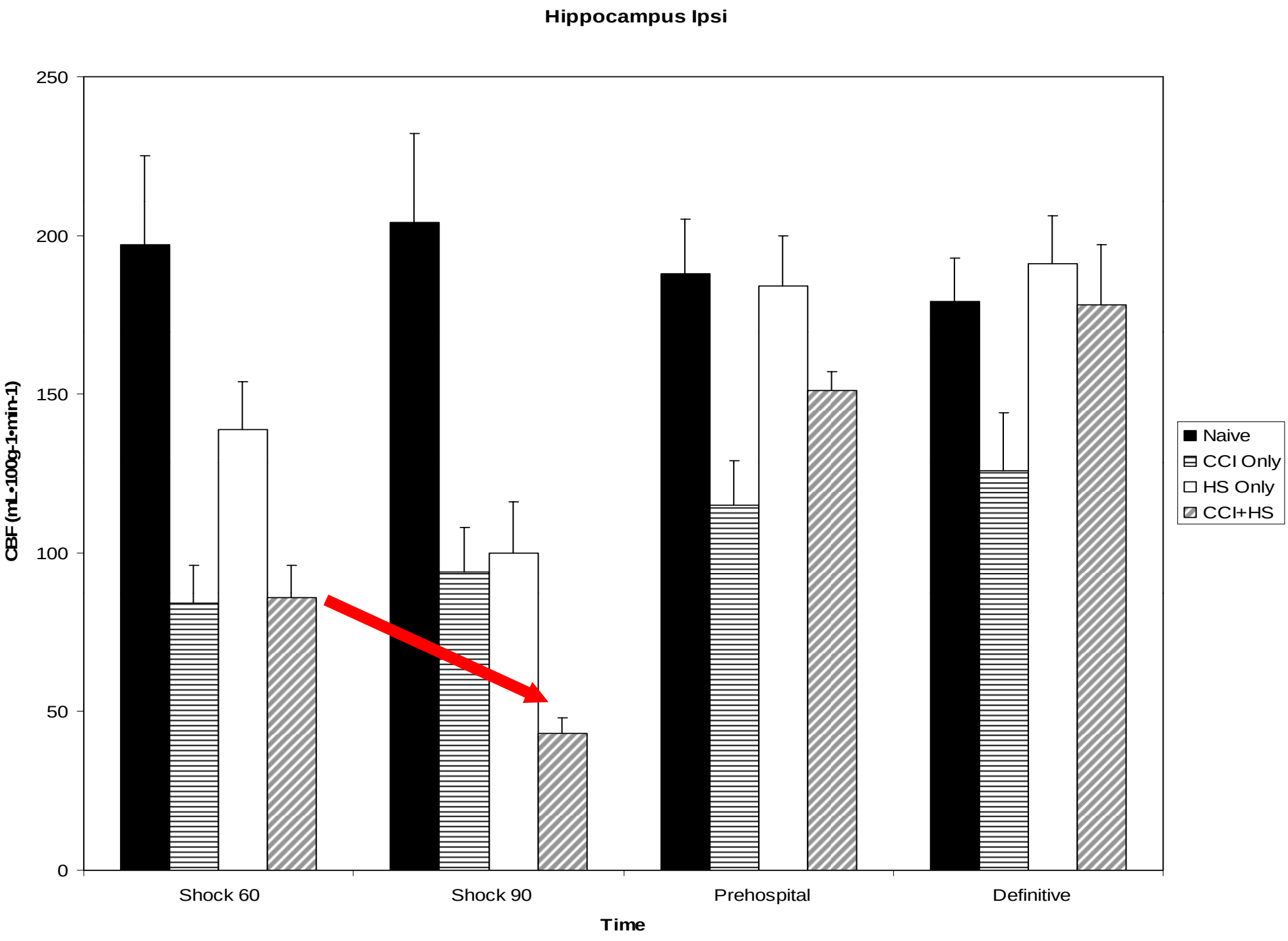
Model – Tissue Oxygenation

Mouse model of CCI + HS—LR resuscitation



Naïve
TBI only
TBI + HS

Shock	Pre-hospital	Definitive care


Hippocampus Ipsi
250
200
150
100
50
0
CBF (mL•100g-1•min-1)
Shock 60
Shock 90
Prehospital
Definitive
Time
Naive
CCI Only
HS Only
CCI+HS

Safar Center DOD Interface: Current/Pending

Safar Center TBI Program

Novel Nitroxide-based TBI resuscitation
Peer-reviewed medical research program
P. Kochanek, MD, PI

Biomarkers in TBI
CDMRP Concept award
Amy Wagner, MD

PREVENT blast program Phase II; DARPA
Richard Bauman, PhD, PI
COL Geoff Ling, MD, Program Manager
P. Kochanek, MD Site PI

Calcineurin and TBI
Veterans Administration
C. Edward Dixon, PhD, PI

Oxygen, ventilation and TBI resuscitation
COL James Atkins, PhD, PI
CDMRP
P. Kochanek, MD Site PI
G. Fiskum, PhD, U. Maryland

Linking a number of the key Blast programs within the US Army with Pitt and the University of Maryland—and internal therapeutic screening

Neuroprotective therapeutics
COL James Atkins, PI
RAD-2
P. Kochanek, MD Site PI

Nutritional supplements
COL James Atkins, PI
RAD-3
P. Kochanek, MD Site PI

Potential for Further Linking DOD-Civilian TBI Resources via Support of pending OBTT

Brain Dysfunction and Blast Injury
COL James Atkins, PhD, PI
WRAIR
P. Kochanek, MD Site PI

PREVENT blast program
DARPA
Richard Bauman, PhD, PI
COL Geoff Ling, MD, Program Manager
P. Kochanek, MD Site PI

Safar Center TBI Program

Operation Brain Trauma Therapy
CDMRP
P. Kochanek, MD, PI

INTRuST
TBI/PTSD
Clinical Consortium
P. Kochanek, EAB

WRAIR Neuroscience
F. Tortella, PhD

Virginia Commonwealth Univ.
J. Povlishock, PhD

Miami Project
W. Dietrich, PhD

Banyan Biomarkes
R. Hayes, PhD

Mission Connect
Houston, TX
TBI/PTSD
Consortium
P. Kochanek, EAB

Linking a number of the key Blast and penetrating TBI programs in the US Army with a nationally renowned multi-center therapy screening consortium (OBTT)

New Grants Funded 08/09 Academic Year and beyond

19 new grants—12 faculty and 1 fellow

- **Hulya Bayir, MD—First RO1 (NICHD)**
- **Hulya Bayir, MD—New R21 (NINDS)**
- **Rachel Berger, MD, MPH—First RO1 (NICHD) [09/10]**
- **Robert Clark, MD—RO1 competitive renewal (NINDS) [09/10]**
- **Robert Clark, MD—New RO1 (Combination therapy in TBI RFA, NINDS) [09/10]**
- **C. Edward Dixon, PhD—New VA Merit Award**
- **C. Edward Dixon, PhD—RO1 competitive renewal (NINDS)**
- **Tomas Drabek, MD—New American Heart Assoc, Beginning grant in aid [09/10]**
- **Ericka Fink, MD—New K23 (NINDS) [Kochanek]**
- **Ericka Fink, MD—New Laerdal Foundation Grant in Aid**
- **Andreas Janata, MD—New Peter Safar Fellowship grant, Laerdal Foundation [09/10]**
- **Andreas Janata, MD—New Laerdal Foundation Grant in Aid [09/10]**
- **Larry Jenkins, PhD—RO1 competitive renewal**
- **Anthony Kline, PhD—New RO1 (NICHD/NCMRR)**
- **Patrick Kochanek, MD—New DARPA Prevent Phases I and II**
- **Patrick Kochanek, MD—New CDMRP Intramural—US Army TBI Consortium**
- **Mioara Manole, MD—New K08 (NICHD) [Clark]**
- **Samuel Tisherman, MD Congressional Appropriation/TATRC/US Army**
- **Amy Wagner, MD—New CDMRP Extramural—Concept award**

Safar Center: Special Programs

Strong and Unique Interaction with DOD

University Brain Trauma Research Center
BRTC—Ed Dixon, PI
PPG from NINDS
in its 14th year

and Resuscitation Research
T-32 from NICHD
P. Kochanek, PI
in its 10th year

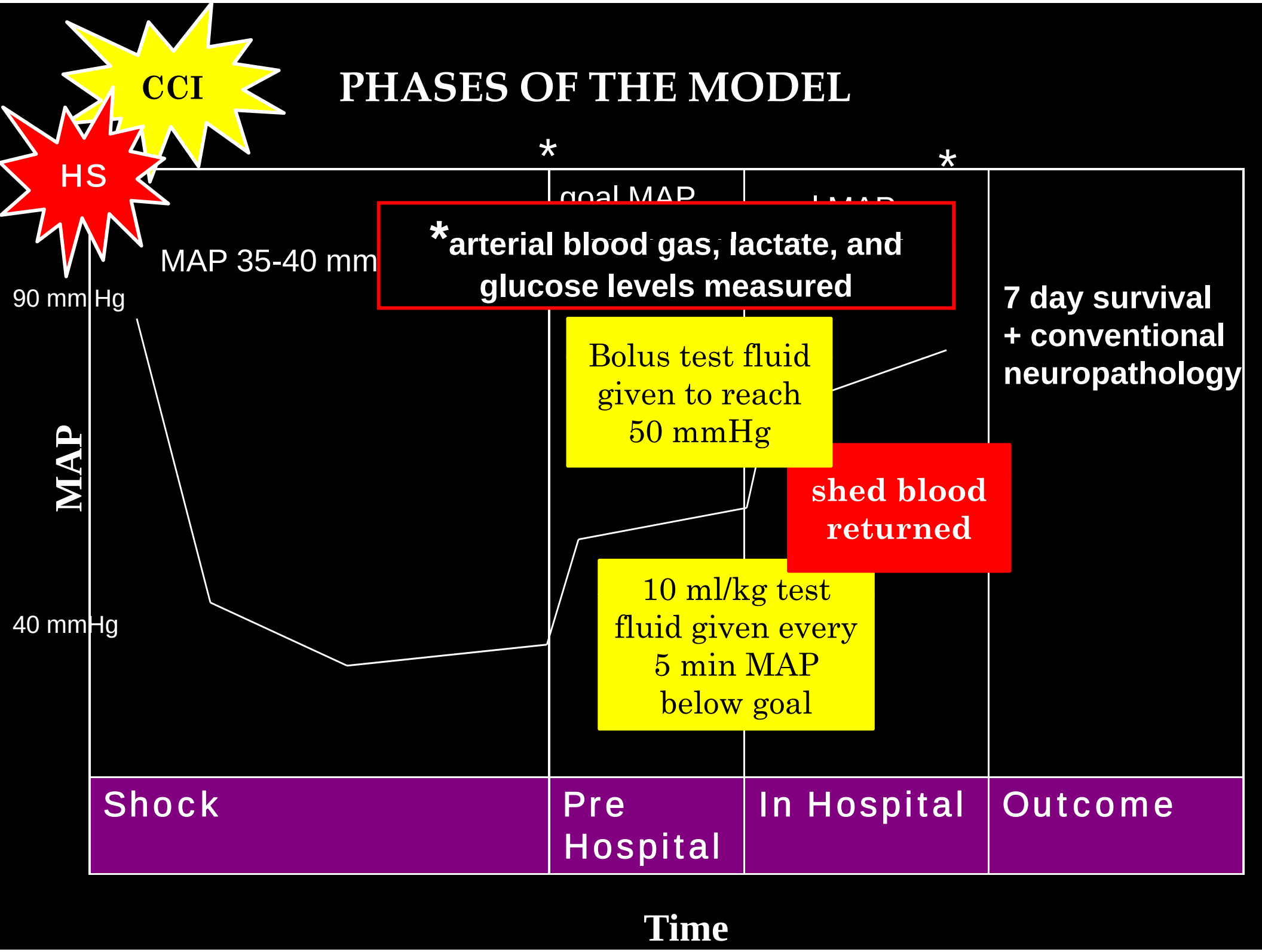
US Army
PPG on TBI Resuscitation
P. Kochanek, PI
Collaboration with
SynZyme technologies
Year 4

DARPA PREVENT
Multi-center collaborative
Program with WRAIR,
Harvard, Yale, USUHS &
Safar Center
In its 2nd year
P. Kochanek, PI

SAFAR CENTER FOR RESUSCITATION RESEARCH
UNIVERSITY OF PITTSBURGH

US Army
Regional TBI Consortium
WRAIR Brain Dysfunction
and Blast Injury Program,
Maryland Shock Trauma,
& Safar Center
Newly Funded
P. Kochanek, PI

Two NIH-funded
Clinical Trials
of Mild Hypothermia
At CHP
TBI (Bell)
Asphyxia (Fink)

Emergency Preservation
and Resuscitation (EPR)
Clinical trial for ultra-advanced
trauma resuscitation
with Maryland Shock Trauma
TATRC (Tisherman)

PHASES OF THE MODEL