



Combat Casualty Care Research Program

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BRIEFING TOPICS



- **Mission, Focus Areas and Drivers**
- **Personnel & Funding**
- **Research Portfolios**
- **Three Successes**
- **Three Challenges**
- **Plans and Summary**

Combat Casualty Care Research Program



Mission



To reduce the mortality and morbidity resulting from injuries on the battlefield



Combat Casualty Care Research Program



Key Focus Areas



- Mortality
 - **Non-compressible Hemorrhage**
 - Including Coagulopathy
 - Compressible Hemorrhage
 - Extremity
 - Axilla/neck/groin
 - Pneumothorax
 - Airway Compromise
 - Multisystem Organ Failure
 - Sepsis
 - Deep Vein Thrombosis
 - Other
- Morbidity
 - **TBI**
 - Mild to Severe
 - Massive Soft Tissue Injury
 - Orthopedic Trauma
 - Spine trauma
 - Spinal Cord Injury
 - Mangled extremity
 - Burn
 - Craniofacial Injury
 - Pain (acute and chronic)
- Training
 - Medic
 - Specialty Surgeon
 - Other Providers

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Combat Casualty Care Drivers-1



84% of potentially preventable deaths are due to uncontrolled hemorrhage

Kelly et al., J Trauma, Feb 2008 Suppl

20% of combat casualties require a blood product transfusion

McLaughlin et al. J Trauma 64:S57, 2008

Reduce the Number of Deaths on the Battlefield

- Damage control resuscitation
 - ✓ Clotting factors (prothrombin complex concentrates, fibrinogen, etc.)
 - ✓ Freeze-dried plasma, other blood products
- Enhanced resuscitation fluids

Reduce Morbidity and 'Died of Wounds' Rate

- Full physiologic life support systems
- Hypoxic injury reduction

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Combat Casualty Care Drivers-2



**RAND “Invisible Wounds of War”, 2008
up to 320,000 with at least mild TBI**

**Adverse events in patients evacuated by
helicopter:**

Lehmann, J Trauma, 66:S31-S36, 2009

38% cardiac arrhythmia

17% hypotension

7% hypoxemia

Limit Brain Damage

- Biomarkers
- Diagnostic/Monitoring devices
- Oxygen delivery methods (e.g. Perfluorocarbons)
- Neuroprotective drugs

Improve En Route Care

- Oxygen conservation
- Closed loop algorithms
- Lightweight modules
- Improved litter systems

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Combat Casualty Care Drivers-3



35,831 total wounded in OIF/OEF
16,491 wounded not returned to duty

<http://www.defenselink.mil/news/casualty.pdf> (2009)

**For every injured soldier not returned to
duty there are 2.3 extremity wounds =
37,929 wounds**

Owens et. al., J Orthop Trauma 21:4, 2007

**16% of all war related injuries are
maxillofacial, head, and neck injuries**

cited in Hale, J Trauma, 64:S265-276, 2008

Meet Demands on First Responders

- Decision-assist tools

Acute Care of Battle Injuries

- Orthopedic Trauma
- Maxillofacial Trauma
- SCI/Spine trauma
- Pain

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Combat Casualty Care Drivers-4



Dismounted Complex Blast Injury

In 2008, the Afghanistan Theater of Operation monthly Battle Injuries exceeded that seen in the Iraq Theater of Operation, and the associated trend lines have continued to diverge.

Our focus is to minimize morbidity associated with the initial explosive injury, and to present the patient in an optimal physiological state for long-term rehabilitation and functional recovery.

2011 REPORT OF THE ARMY DISMOUNTED COMPLEX BLAST INJURY TASK FORCE

CCCRP DCBI Key Tasks

PRE-HOSPITAL CARE

- Pre-hospital plasma
- Tranexamic acid
- Fluid resuscitation
- Hemostatic Agents
- Physiological Monitors
- Improved tourniquets
- Perfluorocarbon O₂ delivery

ACUTE RESUSCITATION

- Dried Plasma

DEFINITIVE HOSPITAL CARE

- Restoration of peripheral and central nerve function

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Personnel AND FY2011 FUNDING



PERSONNEL

Military	Civilians	IPAs	On-site Contr.	TOTAL
3	8	4	4	19

FY2011 FUNDING \$K

	Army S&T	Army Adv Dev	DHP RDT&E	CRADAs	TOTAL
MRMC Core	45820	11160			56980
MRMC CSI			89386		89386
DHPe			60736		60736
External Partners				4485	4485

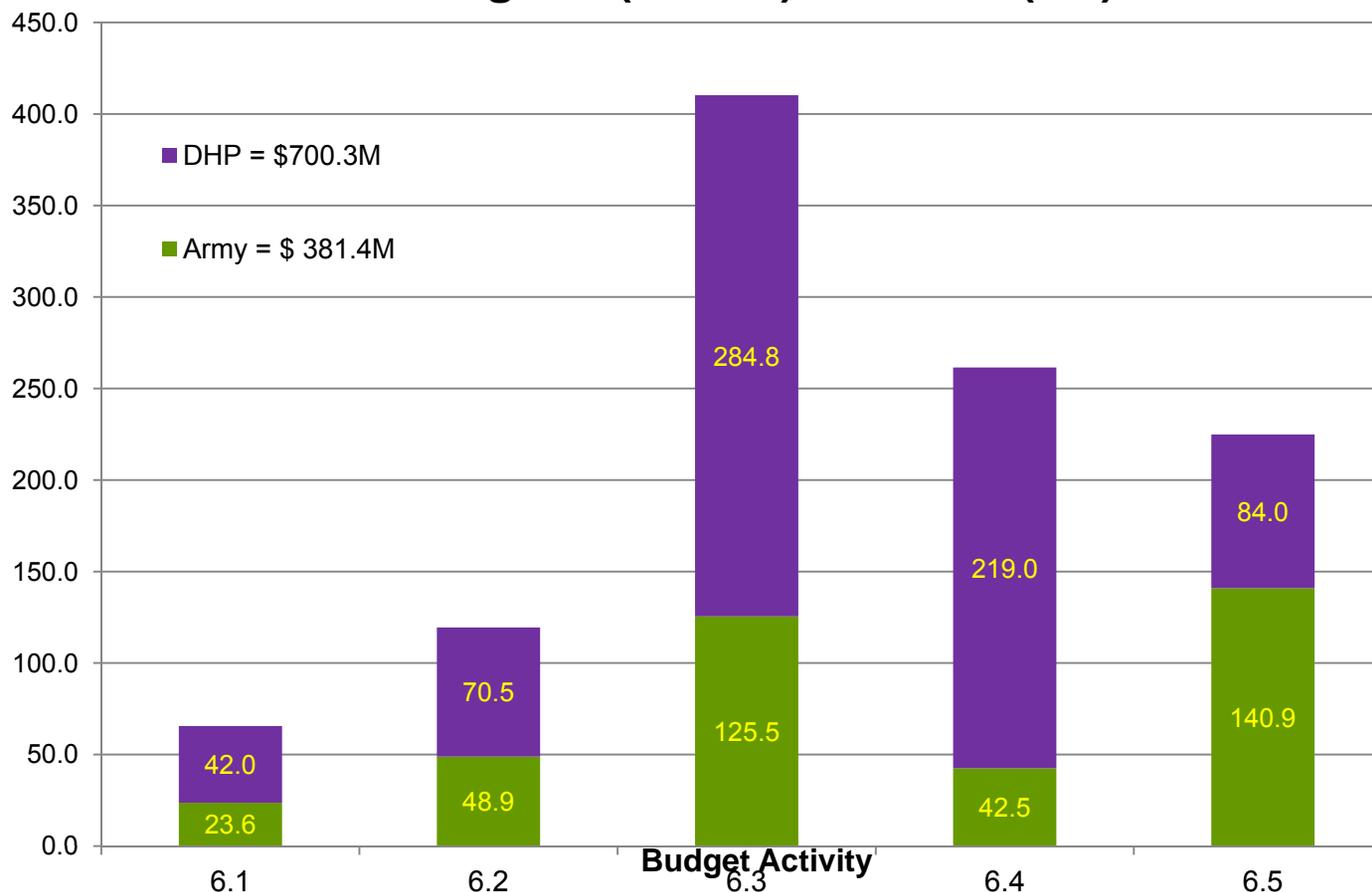
GRAND TOTAL: ~\$212M

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Army/DHP Program Distribution (FY14-18)

Total Program (6.1-6.5) FY14-18 (\$M)



Combat Casualty Care Research Program



Combat Casualty Care Research Portfolios



Hemorrhage and Resuscitation

Traumatic Brain Injury

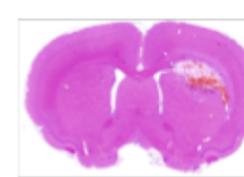
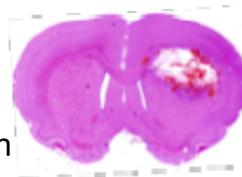


- Hemorrhage Control
- Blood Products
- Complement Inhibition
- Resuscitation Fluids

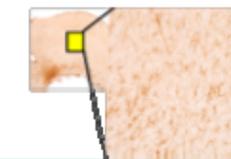
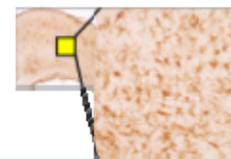
USAISR

Vehicle

NNZ-2566



- Penetrating Injury
- Diagnostic Device
- Neuroprotective Drug



- Blast Effects
- WRAIR*

Forward Surgical/Intensive Care

Treatments for Tissue Injury



- Trauma Vitals
- Critical Care Technology
- Decision Support
- Closed Loop Control

USAISR



- Maxillofacial Injury
- Ocular Trauma
- Pain Control
- Burn Treatment

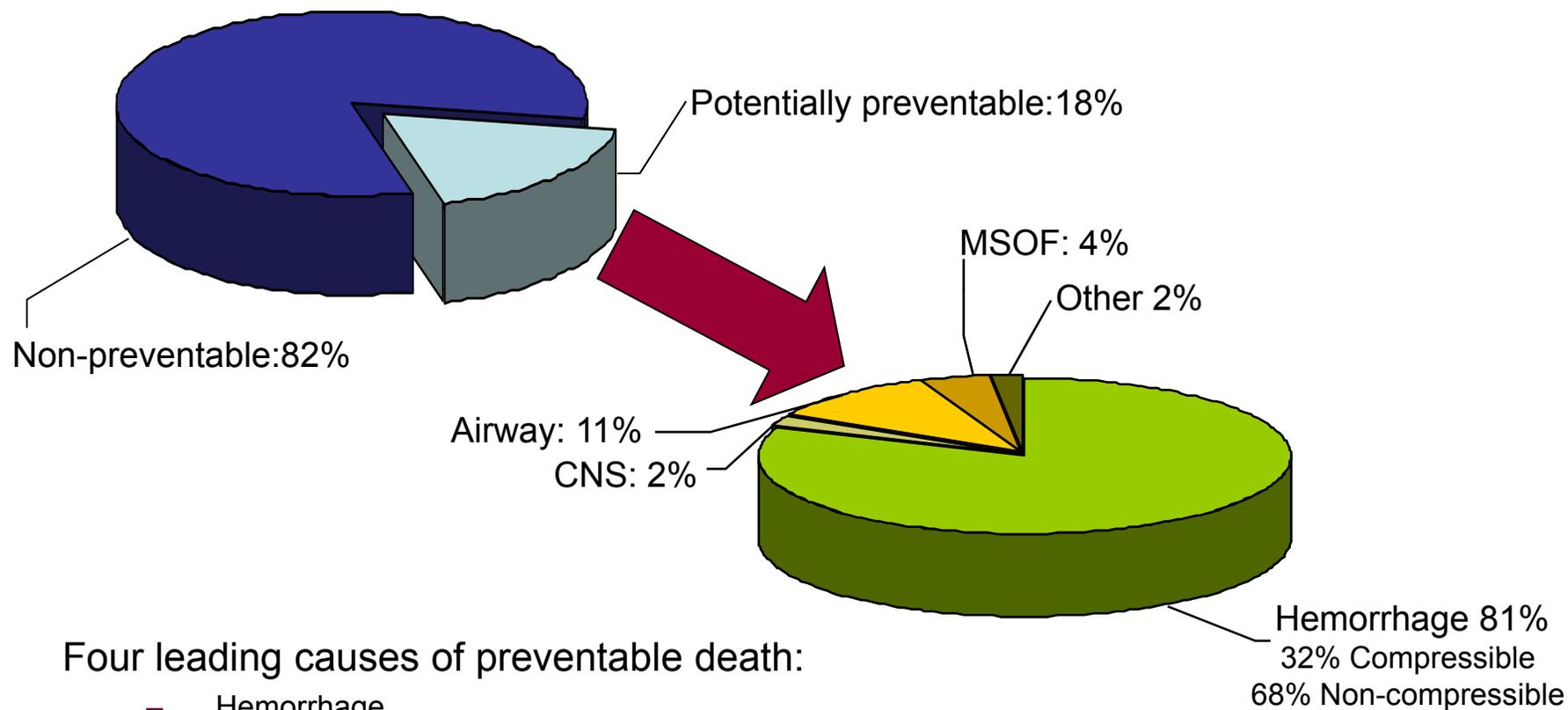
USAISR



Hemorrhage and Resuscitation Research and Development Program



Causes of Death on the Current Battlefield



Four leading causes of preventable death:

- Hemorrhage
- Airway Compromise
- Tension Pneumothorax
- Hypothermia

Martin et al., 2009, J Trauma



Hemorrhage and Resuscitation



Program Scope and Purpose

- **Scope:** The Hemorrhage and Resuscitation R&D program includes DoD efforts in the general areas of hemorrhage control, fluid resuscitation, blood products, transfusion, and pathophysiologic responses to traumatic hemorrhage, with a view ranging from basic and discovery research through clinical development
- **Purpose:** Conduct research and development to provide improved methods, drugs, and devices to stop bleeding, restore lost blood volume, and mitigate the consequences of hemorrhage. Reduce mortality by up to 16% overall.

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Major Efforts



Major Effort	Goal
Improved Blood Products	Develop safer and more logistically supportable blood products for transfusion
Damage Control Resuscitation	Identify the best ways to use existing and newly developed blood products, drugs, and fluids (Including Transfusion Practices using existing products-CPGs)
Coagulopathy of Trauma	Identify diagnostic and therapeutic targets to prevent or treat coagulopathy of trauma
Immune/Inflammatory Modulation	Evaluate promising approaches to modulate inflammatory responses of the patient
Metabolic and Tissue Stabilization	Evaluate promising approaches to modulate/stabilize metabolic responses (Including oxygen delivery)
Hemostatics	Evaluate/identify existing products and develop new products or procedures to control bleeding

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Traumatic Brain Injury Research and Development Program



Neurotrauma Research



Program Scope and Purpose

- **Scope:** Research on the impact of trauma in military settings on the central nervous system across the continuum of care from basic science, through screening, diagnosis, treatment, rehabilitation and return to duty.
- **Purpose:** Conduct research that leads to the development of improved diagnostics, novel pharmaceuticals or other therapeutic measures and doctrine resulting in measurable improvement in accurate diagnosis and evidence based return to duty decisions and long term outcomes

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Major Efforts

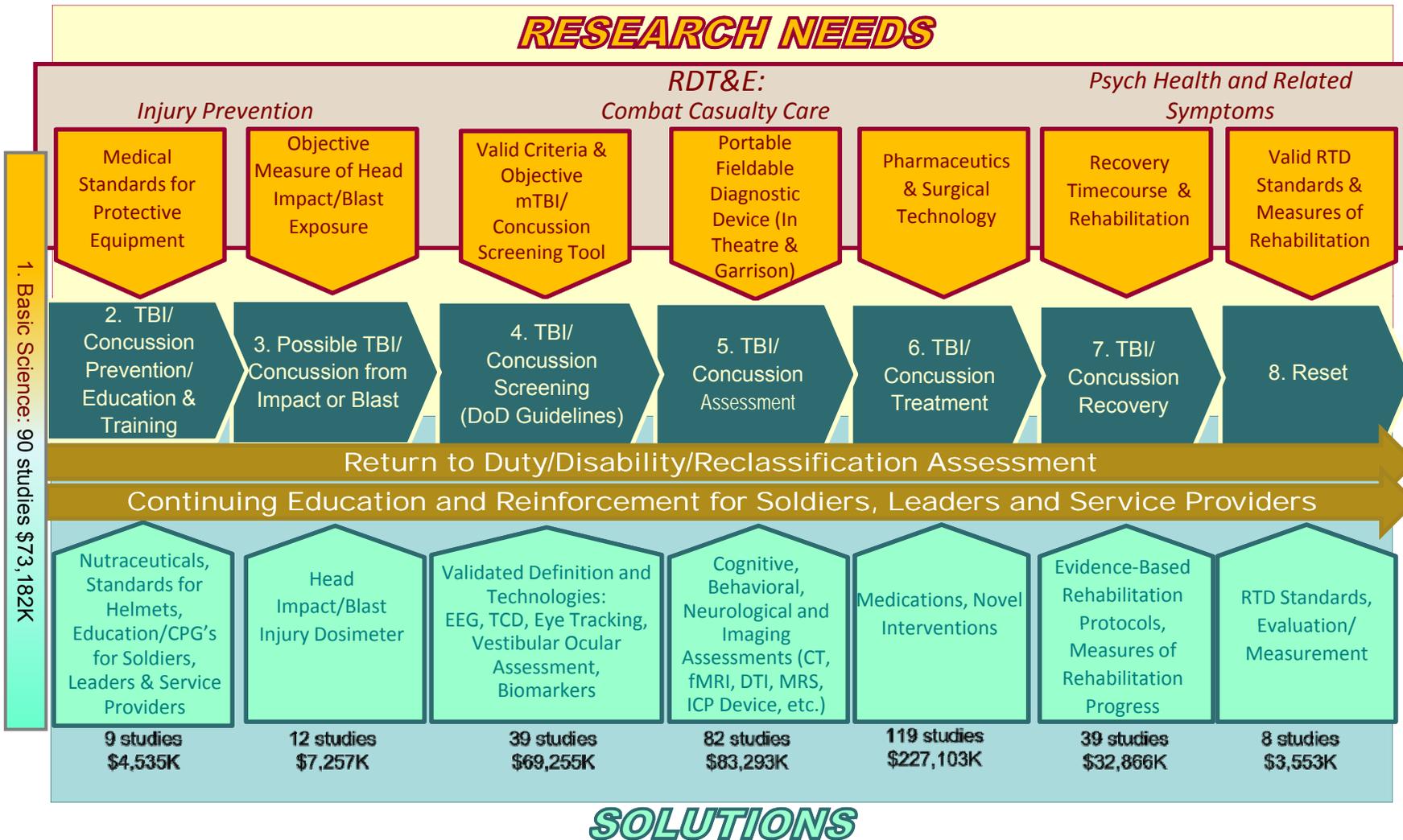


Basic Science	Mechanisms of Damage and Targets for Therapy-molecular to systems Development and validation of animal and computational models (Impact and Impact Plus Polytrauma, Blast and Blast Plus, Primary thru Quaternary Blast)
Screening and Diagnostics	Serum/CSF biomarkers Non-Invasive field based neurodiagnostics (esp mTBI) Non invasive field and transport based neuromonitoring Imaging (structural, functional) CT, MRI (MRS, DTI, SWI, fMRI) etc
Therapeutics (Cognitive Rehabilitation is a separate sub-portfolio)	Standardization Labs/collaborative networks for assessment of new drugs/therapies Comparative Effectiveness Research-outcomes and metrics TBI Pharmacotherapy: Clinical Trials (mono and combination therapy) New drugs or new applications of drugs/new molecular entities Oxygen - Role and use Traumatic Cerebral Vasospasm-Management and prevention Hypothermia - Role and use Regenerative medicine Post trauma seizure/epilepsy Reversal of Disorders of Consciousness
Initial and En-Route Care	Effects of hypovolemic resuscitation on secondary TBI Effects of vibration, G-forces and hypobaria on secondary TBI

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Continuum of TBI Care Determines Research Approach





Forward Surgical/Intensive Critical Care Research and Development Program



Forward Surgical/Intensive Care



Scope: The Forward Surgical/Intensive Critical Care program investment is in key, military relevant gaps across a broad range of research areas including pre/out-of hospital care, emergency care, surgical care, intensive care, nursing care, advanced monitoring, and battlefield medical equipment.

Purpose: Conduct research and foster development to expand knowledge and develop new algorithms, devices, and procedures that advance the decision-making capabilities of medical personnel and promote earlier intervention in pre-hospital, emergency room, and intensive care combat casualty management



Major Effort	Goal
Burn Resuscitation Decision Support System	Implement burn decision support software on a dedicated tablet PC to assist the provider with fluid resuscitation.
Noninvasive Metabolic Sensors for Trauma Care	Test noninvasive sensor for triage and guide to resuscitation in advanced laboratory and clinical settings.
Heart Rate Entropy for Trauma Triage	Develop heart rate entropy as a reliable trauma triage tool for detection of occult and non-occult injuries
Decision Support And Closed-loop Control Of Ventilation For Combat Casualties	Develop an algorithm for closed-loop control of minute ventilation based on End-tidal carbon dioxide (EtCO ₂). Software to control respiratory rate and tidal volume in an open/closed loop fashion



Remote Trauma Outcomes Research Network



(RemTORN)

“Smart” monitor – blood volume

Telemedical direction of 1st responders



Civilian and Military Patients
Follow Similar Pathways



Identify risk for Non-Compressible Torso Hemorrhage

Enable forward blood product transfusion by medics

Out-of-Hospital Phase

Reduce Killed-in-Action rate by 25%



• *Identify linkage between early performance of life saving interventions and extension of the Golden Hour*

• *Develop solutions for predicting and temporizing Non-Compressible Torso Hemorrhage*



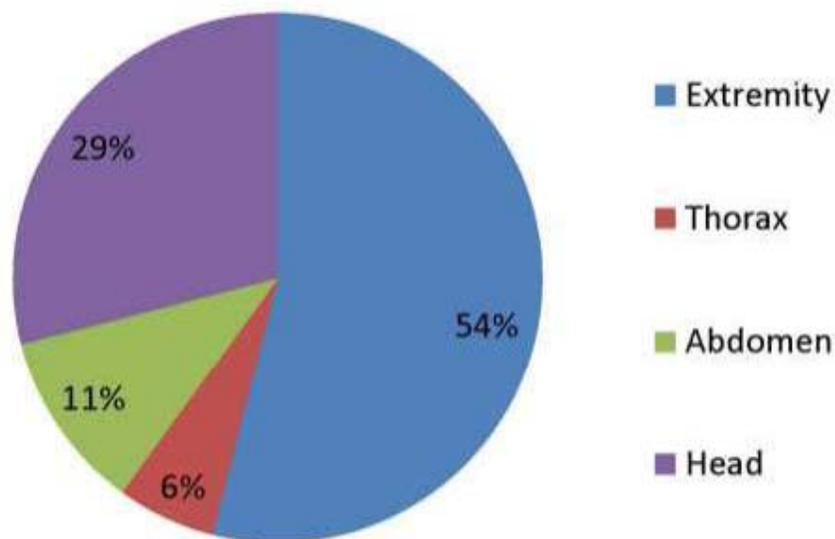
Treatments for Tissue Injury Research and Development Program



Treatments for Tissue Injury



Injury Incidence¹



1. Owens BD, Kragh JF, Wenke JC *et al.* Combat wound in Operation Iraqi Freedom and Operation Enduring Freedom. *J Trauma.* 2008. 64: 295-299.



Treatments for Tissue Injury



Program Scope and Purpose

Scope: This portfolio's research covers the time from point of injury to initial discharge, essentially all modalities administered prior to the patient entering the reconstruction/rehabilitation setting. The primary functional areas for this portfolio include:

- Orthopaedic and extremity trauma,
- Wound care
- Advanced care for burns
- Craniomaxillofacial injuries
- Smoke inhalation and lung injury

Purpose: Coordinate research activities to provide enhanced methods, drugs, technology applications and devices to improve outcomes in the injured warfighter as they proceed through the continuum of care.

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Major Efforts



Orthopaedic Focus Area	Support the Skeletal Trauma Research Consortium's efforts to prevent and treat post-traumatic osteoarthritis Develop a modular, interoperable, three-degrees-of-freedom, externally powered prosthetic wrist with a one-degree-of-freedom terminal device and accompanying control strategies Engineer muscle constructs for repair of traumatic Volumetric Muscle Loss (VML)
Wound Care Focus Area	Continue research to prevent/treat mixed-species biofilm induced impairment of wound healing and regeneration, focusing on recurrent wound infections Use WoundFlow system for wound healing modeling and prediction
Burn Injury Focus Area	Care for the Critically Injured Burn Patient Evaluate methods and products to improve patient outcomes through enhanced clinical practice guidelines Determine mechanism for heterotrophic scarring
Craniomaxillofacial injuries	Determine the stem cell-derived trophic factors or other biological agents capable of actively resolving inflammation, re-establishing homeostasis, limiting excessive tissue injury, and minimizing the development of chronic inflammation
Smoke inhalation and lung injury	Conduct extracorporeal lung research for modeling of lung ventilation Develop ventilator algorithms based on continuous non invasive measurements

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THREE SUCCESSES



1. Breakthrough discovery in TBI detection

- Biomarkers specific to brain injury
 - Completed 200 patient severe TBI feasibility study
 - Mild and moderate TBI feasibility study near completion
 - 1500 patient pivotal study in mild, moderate and severe TBI patients (study initiated June 2011, expected enrollment completion 4th Q 2012)

2. Drug for treatment of TBI

- Phase II clinical trial
 - Cohort I completed
 - 16/30 patients recruited for Cohort II
 - Currently pursuing exception from informed consent for cohort III
 - Adding 6 additional sites

3. New products fielded to save lives on the battlefield:

- Next 2 slides

Combat Casualty Care Research Program



Post 911 Fielded Products Hemostasis



HemCon Bandage



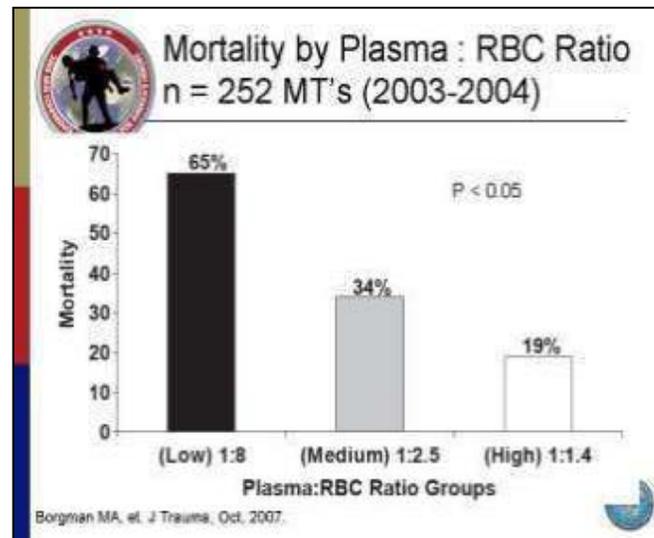
QuikClot



Combat Gauze



Combat Application Tourniquet (CAT)



Plasma Ratio Study



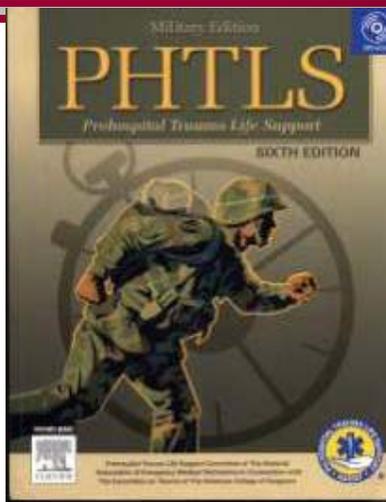
WoundStat



Other Fielded Products



Joint Theater Trauma Registry
Joint Theater Trauma System
Baghdad Research Cell



Tactical CCC adopted



Combat Pill Pack



Hypothermia Prevention and Management Kit (HPMK)



Golden Hour Container



Stand Alone Patient Simulator (METI - iSTAN)



Warrior Aid and Litter Kit (WALK)



Improved First Aid Kit (IFAK)



THREE CHALLENGES



1. New administrative procedures

- Previous planning process was relatively informal
- Developing longer range strategic planning processes
 - Casualty data based, other program aware, broadly focused but prioritized
 - Increased initial work for Program Planning, Task Area Managers & IPTs, POM planning, etc.

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THREE CHALLENGES



2. Historically inadequate funding

- CCCRP historically significantly underfunded
 - Despite significant battlefield requirements for better ways to save lives and reduce morbidity
 - No organized national effort in trauma research, thus limited civilian research to leverage for military trauma
 - Core funding was reprogrammed to CCCRP for FY10 and 11
 - Trauma trials are costly, especially neurotrauma trials
- 20% decrease in core funding in FY12
- DHP Enhancement (GDF) \$\$ are not a replacement for Service programs

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THREE CHALLENGES



3. Integrating multiple programs to efficiently field solutions

Army program Other Service programs

- ONR CCRP
- USAF
- DARPA
- ARL
- ARO
- TATRC
- CDMRP
- USAMEDD DCDD (and Service counterparts)
- JPC6
- MRMC Research Directorates
- USACEHR/Systems Biology
- USAMMDA
- Navy Medical Advanced Development

DHP funding Congressional appropriations

- DoD Blast Injury Program
- TC3
- ASBPO
- DHS
- DMMPO (formerly DSMB)
- USSOCOM
- NHLBI/ROC
- AFECRC SA
- NAMRU SA
- NMRC
- USAISR
- USAMRAA
- WRAIR

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Plans



Near Term
FY 12-14



Determination of optimal plasma to RBC ratio, assessment of specific clotting factors, determine effect of inflammation modulators

Studies on Trauma Induced Coagulopathy

Development of Trauma Outcome Prediction Models and decision assist technologies for ICU applications

New focus on pre-hospital diagnoses and treatments, in-theater trials, non-invasive physiologic signals, Rem(TORN)

Transition soft tissue and bone defect therapies to larger animal models

Develop a maxillofacial wound healing model

Mid Term
FY 15-17



Evaluate and incorporate platelet-derived agents and inflammation modulators into the Damage Control Resuscitation strategy

Develop a diagnostic for coagulopathy of trauma

Develop and refine decision support algorithms for burn resuscitation, ventilation, nutrition, and pressor and blood pressure management

Algorithm to track blood loss under various conditions (heat, cold, dehydration, varying rates of blood loss) and resuscitation in real-time

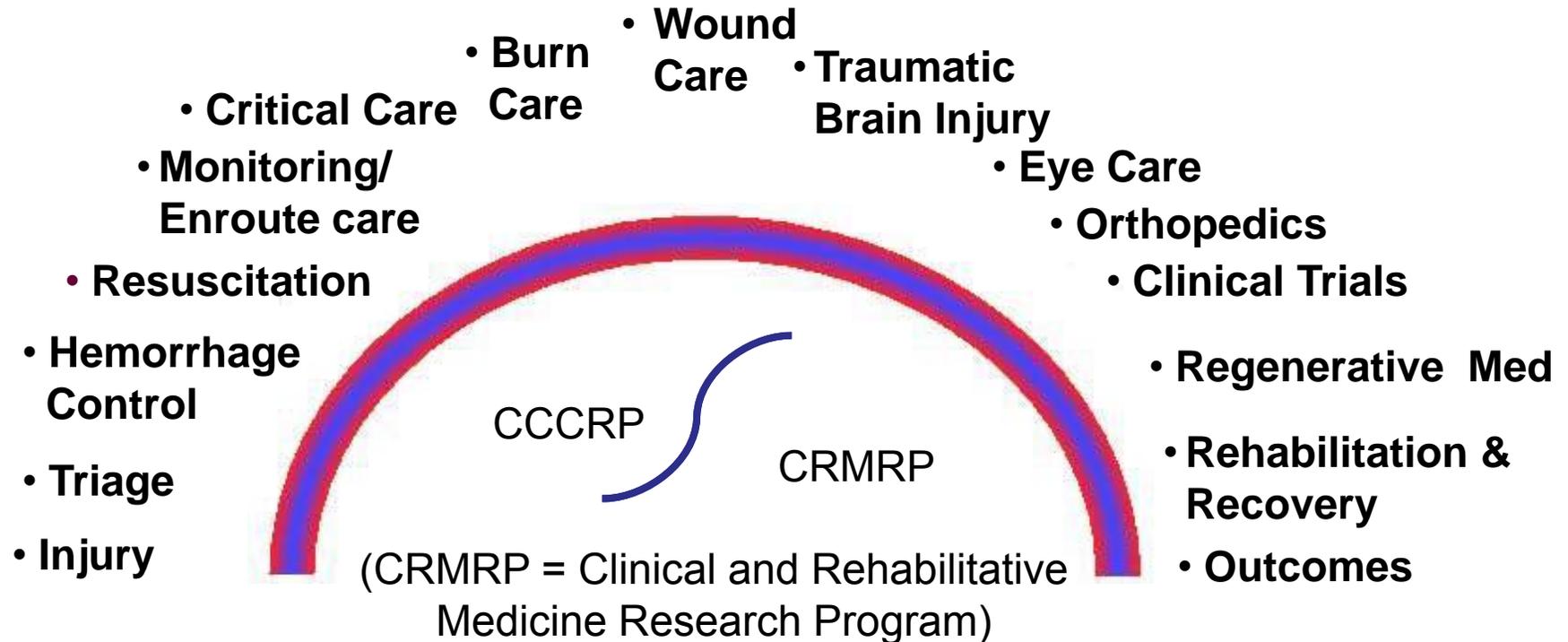
Improve functional outcomes of limb and bone stabilization and repair, wound healing, and functional salvage

Initiate program to research treatments for acute lung injury

Combat Casualty Care Research Program



Summary



MRMC is addressing the spectrum of combat trauma through a prioritized, integrated program with Army and DHP funds in accordance with the guidance from Congress and Military Leadership

Combat Casualty Care Research Program



Backup Slides

Combat Casualty Care Research Program

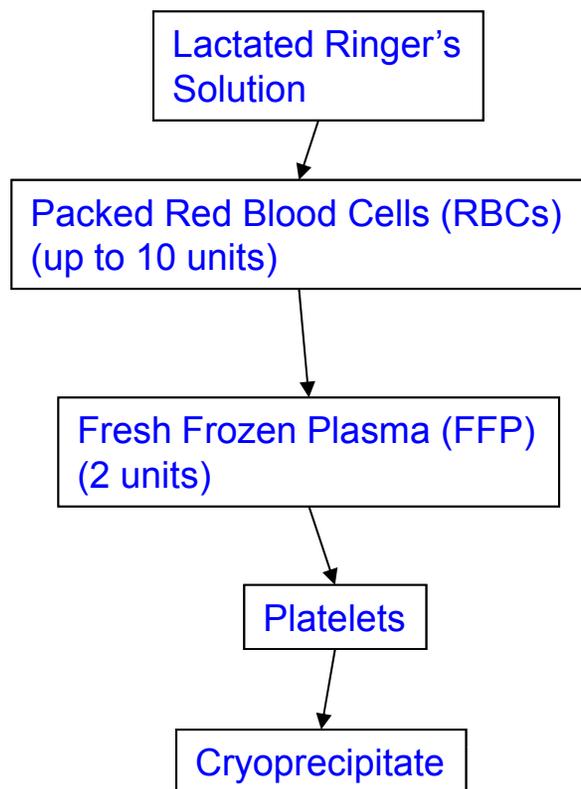


Damage Control Resuscitation

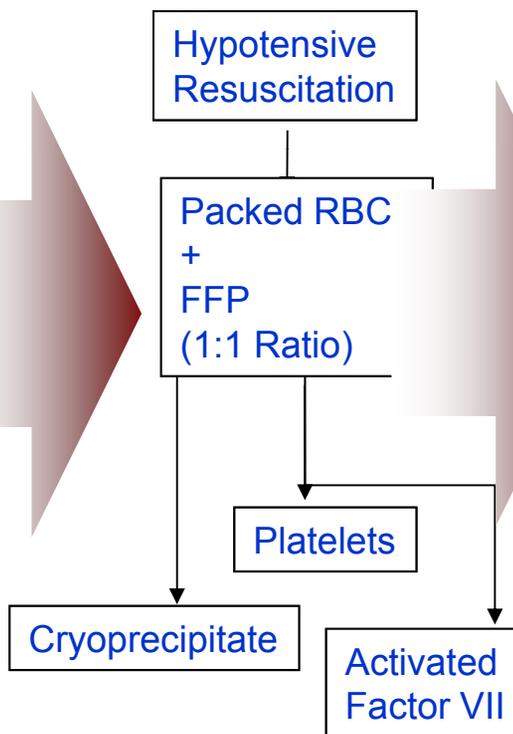


One of Army's "Top Ten Greatest Inventions of 2007"

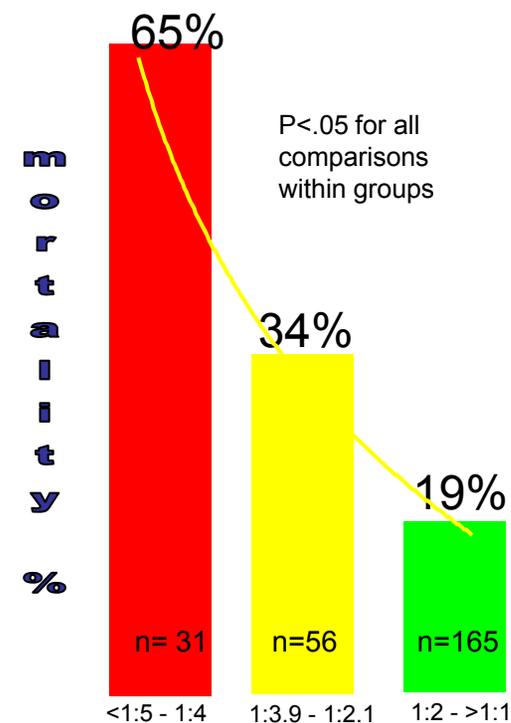
Standard Resuscitation



Damage Control Resuscitation

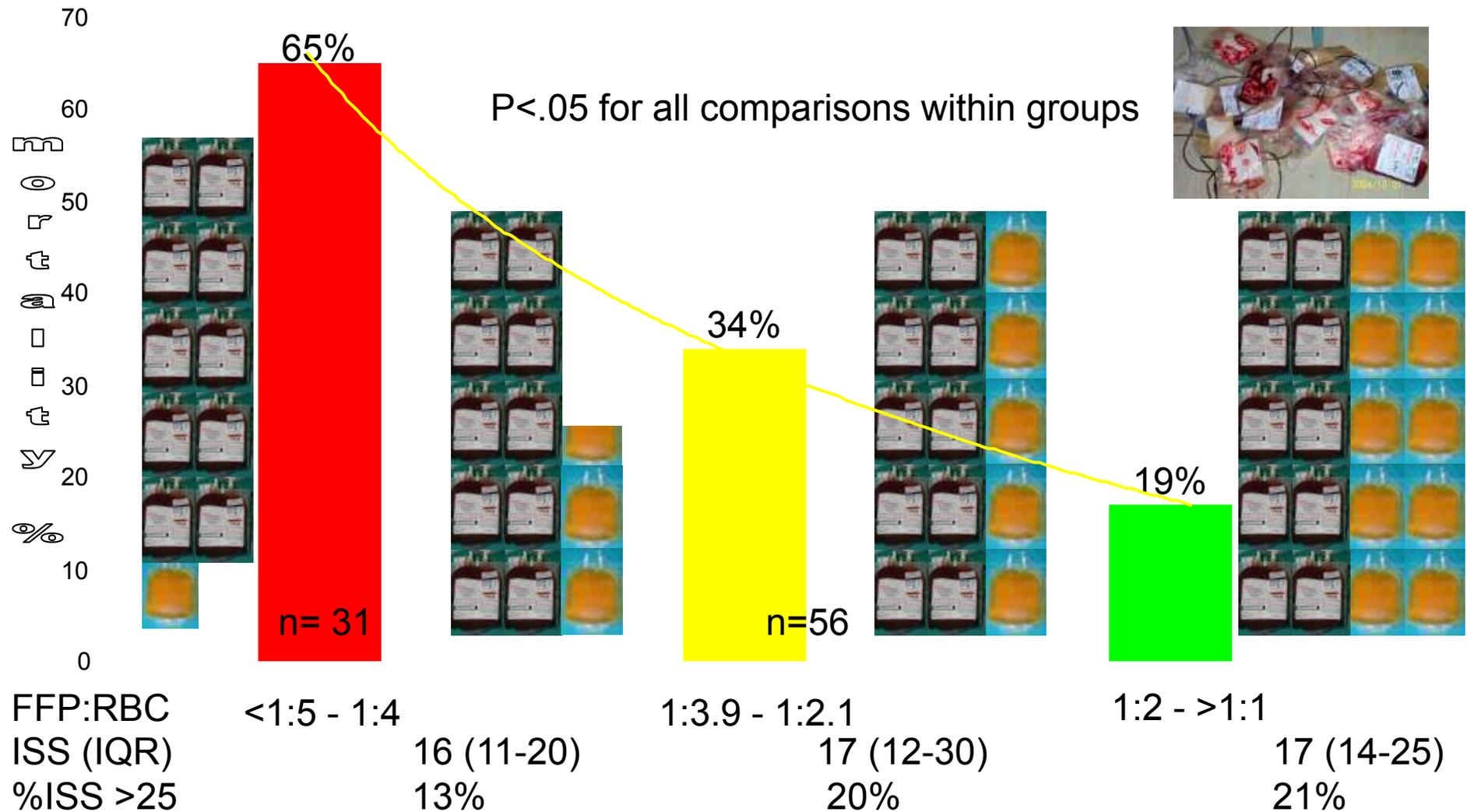


FFP:RBC effect on mortality





FFP:RBC effect on mortality



Borgman et al. J Trauma 63:805, 2007



Damage Control Resuscitation “Blood Products, Hemostasis”



Blood Products:

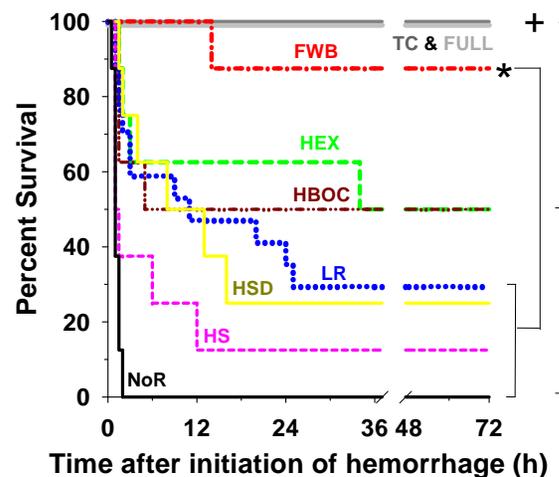
- rFVIIa
- CP Platelets
- FD Plasma
- FD Fibrinogen
- Platelet Derived Hemostatic Agent
- Fresh Whole Blood
- Pathogen Inactivation

Hemostasis:

- Basic research in coagulation
- Testing of new COTS products
- Tests of mixtures of products
- Inflammation's effects on clotting

Resuscitation:

- Complement's effect on resuscitation
- Hemorrhage induced metabolic derangements
- Reverse engineering Fresh Whole Blood
- Resuscitation in head injury and coagulopathy

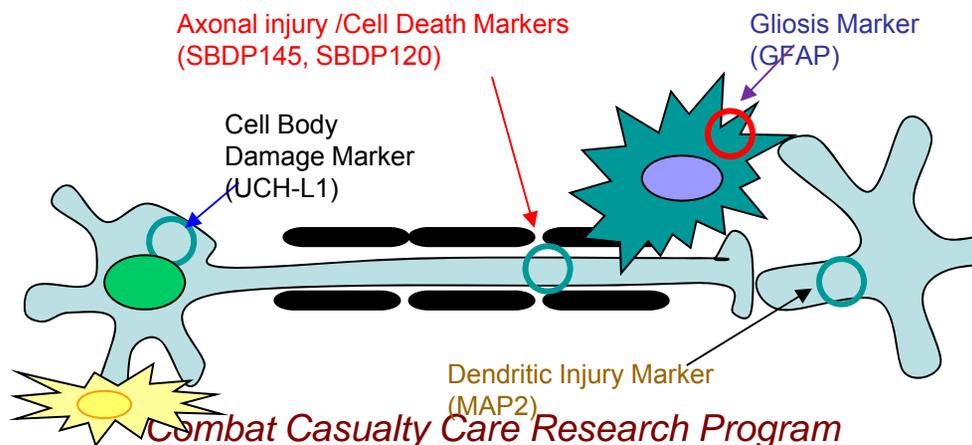




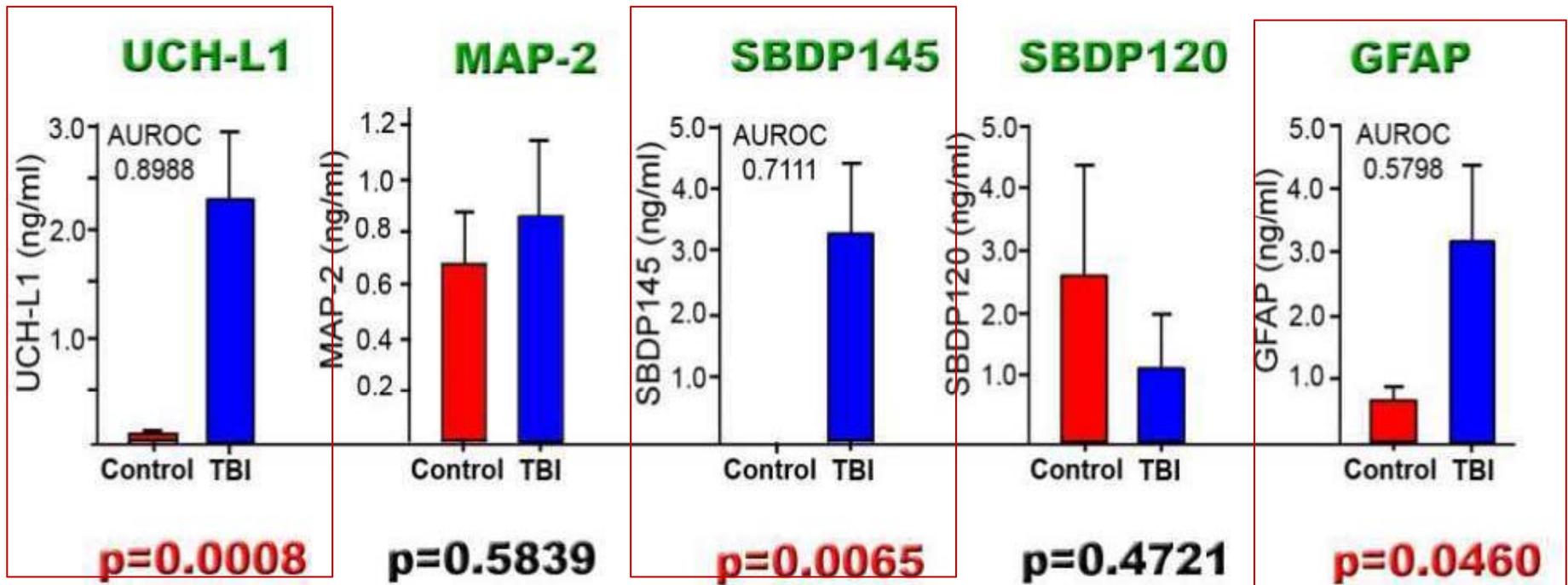
Current Status and Results of BANDITS



SBDP145:	Acute Neural Necrosis (<i>Calpain-mediated</i>)
SBDP120:	Delayed Neural Apoptosis (<i>Caspase-Mediated</i>)
UCH-L1:	Neuronal Cell Body
MAP-2:	Dendritic Marker
GFAP:	Gliosis Marker



Diagnostic Utility of Biomarkers Using First Available Serum Sample



Time to First Serum Sample

Average	10.1 hours
Std Dev	6.96
Minimum	2
Maximum	24

Sample Sizes

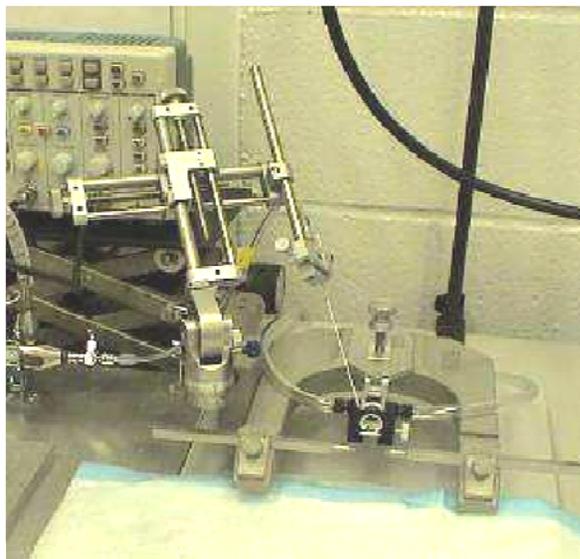
TBI Subjects:	46
Controls (MAP-2, UCH-L1, GFAP)	64
Controls (SBDP145, SBDP120)	10



Drug for Treatment of TBI



Basic Research:
Developed penetrating
head injury model

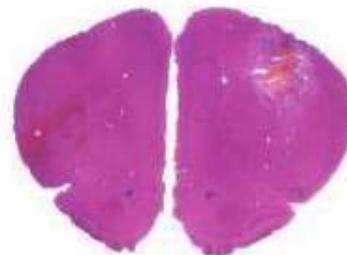


Concept Refinement:
Demonstrated efficacy
in rats

Vehicle



NNZ-2256



Exploratory Development:
Phase II clinical trials

•Phase IIa Safety/Efficacy:

•Start Q1'09

•1st Endpoints:

- Mortality
- Neuromotor Function

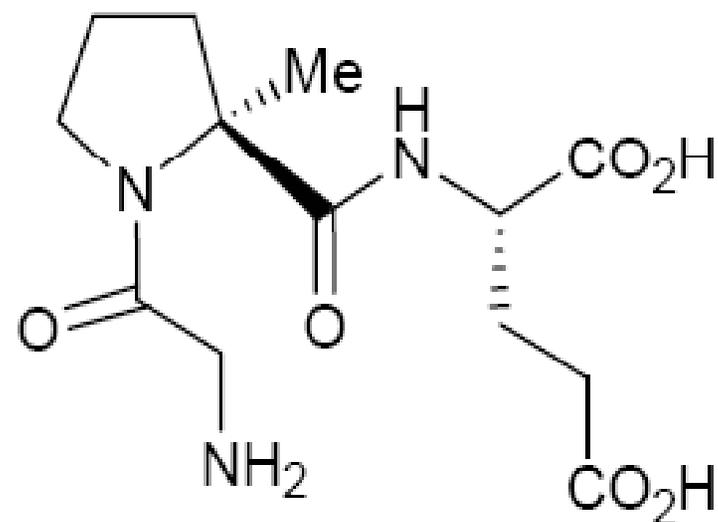
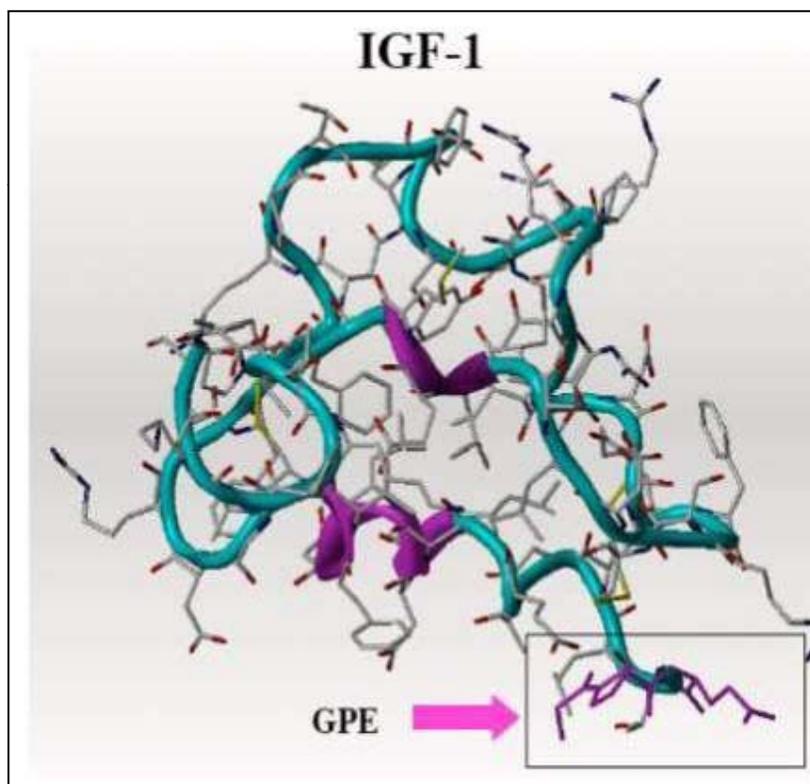
•2nd Endpoints:

- SBS (Silent Brain Seizures)
- BANDITS biomarkers

NNZ-2256 is an analog of Glypromate® (or Glycine-Proline-Glutamate), a naturally occurring small molecule neuroprotectant, derived from IGF-1 (Insulin-like Growth Factor), that is produced in the brain but does not bind to IGF-1 receptors



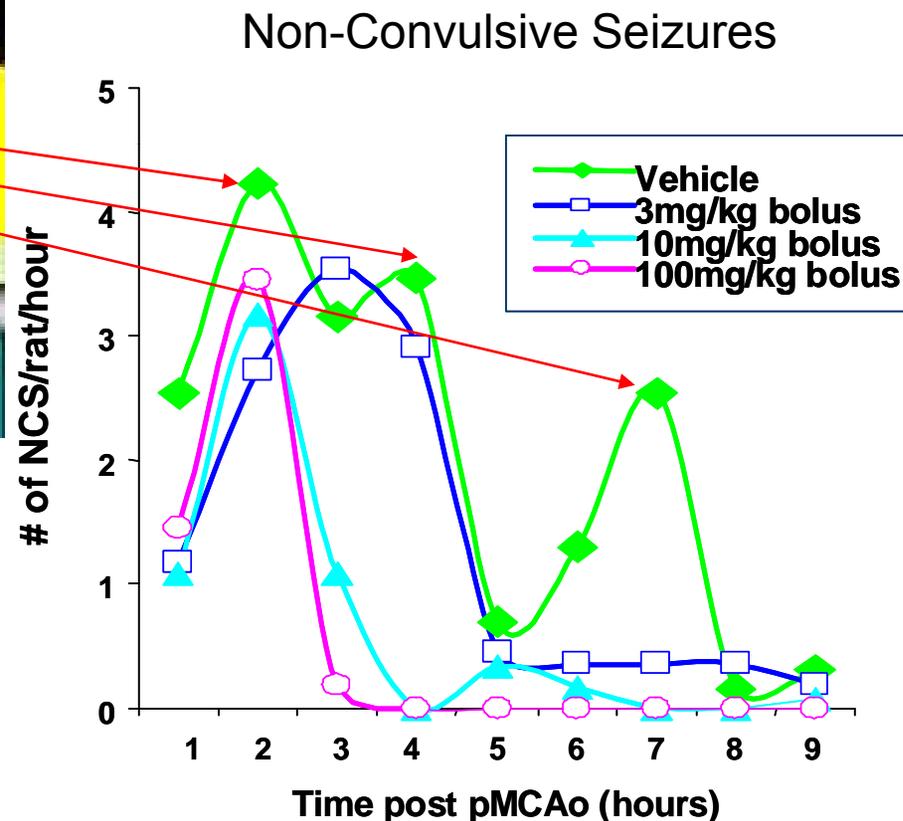
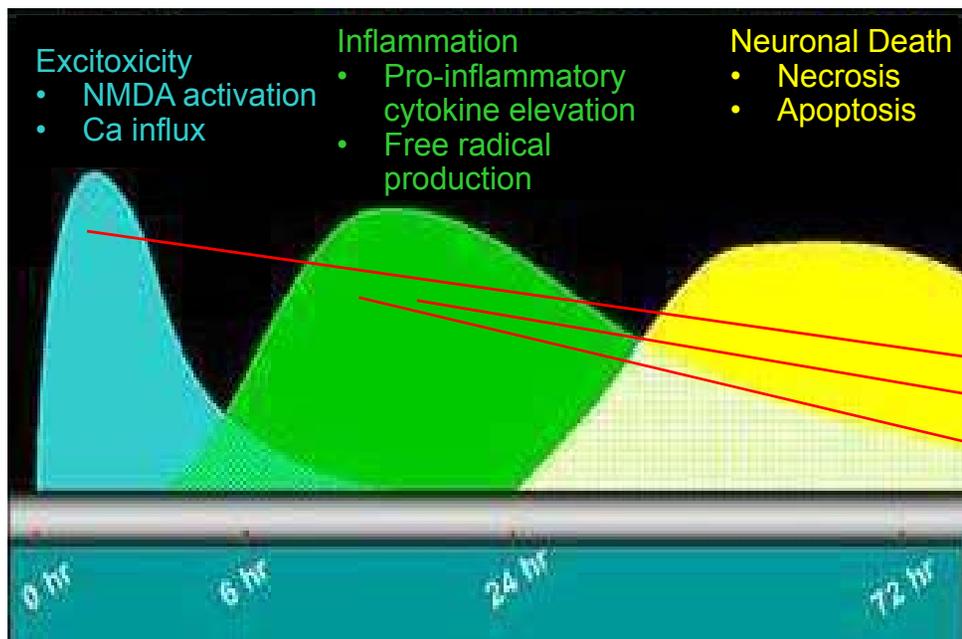
Drug (NNZ2266) for Treatment of TBI



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Non-Convulsive Seizure Time Course



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