WELCOME

MILITARY MEDICAL INDUSTRY DAYS

featuring the

U.S. Army Institute of Surgical Research

Hosted by the

City of San Antonio and
San Antonio Economic Development Corporation

OPENING REMARKS - BACKGROUND

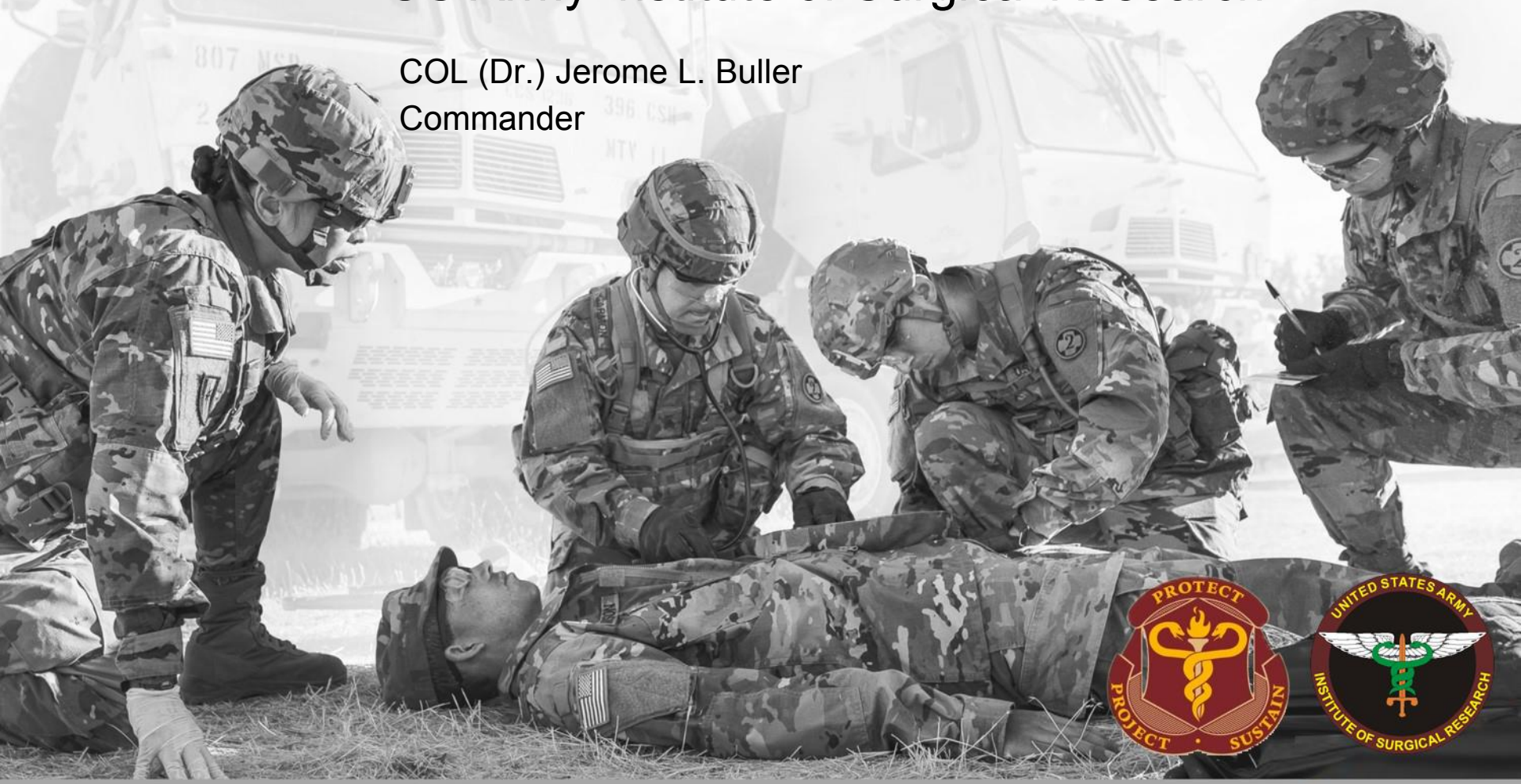
- Why are we here?
- How did we get here?
- What is next?

Ed Davis, Executive Director (ed@saedc.org)
San Antonio Economic Development Corporation

Driving Innovation:
From Military Research to Civilian Medical Practice

US Army Institute of Surgical Research

COL (Dr.) Jerome L. Buller
Commander



Non-Endorsement Disclaimer

"The views, opinions and/or findings contained in this presentation are those of the author and do not necessarily reflect the views of the Department of Defense and should not be construed as an official DoD/Army position, policy or decision unless so designated by other documentation. No official endorsement should be made."

“Reference herein to any specific commercial products, process, or service by trade name, trademark, manufacturer, or otherwise, does not necessarily constitute or imply its endorsement, recommendation, or favoring by the U.S. Government.”

March 2019

Agenda

- Opening Comments
- Historical Perspectives: Standing On The Shoulders Of Giants
- Last 18 Years of War
- The Future

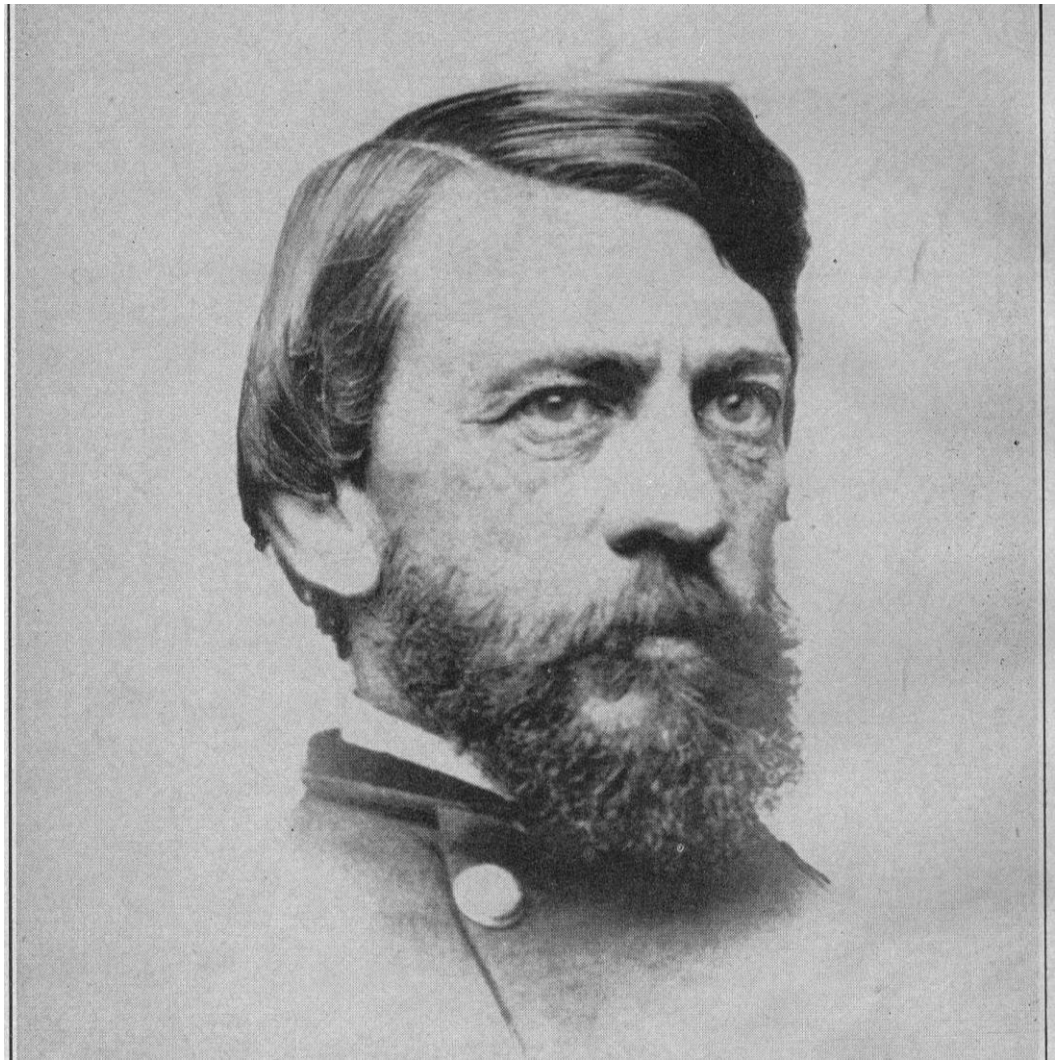
“The only victor in war is medicine.”

Ambrose Pare´

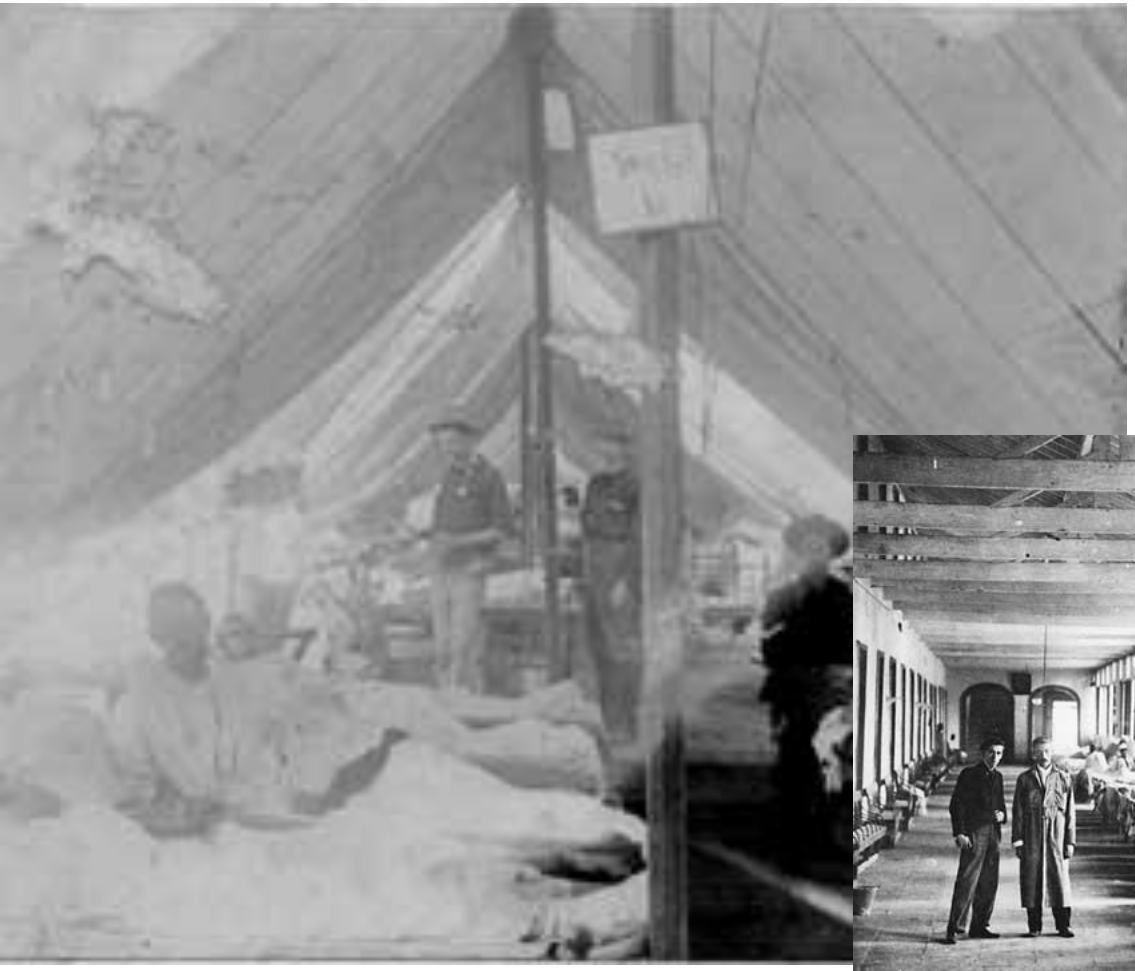
The Civil War: Origin of Trauma Systems

MAJ Jonathan Letterman

- Medical Director, Army of the Potomac (1862)
- Problem: Wounded men were often left on the battlefield for days. (22K / Second Manassas)
- Letterman developed an Ambulance Corps and an effective evacuation system.
  - Triage
  - Field Dressing Station
  - Field Hospitals
  - Large Hospitals
- Impact – Battle of Antietam September 17, 1862 - over 23,000 casualties removed from the field in just 24 hours.



Spanish-American War: The Unseen Enemy



MAJ Walter Reed

- US Army pathologist and bacteriologist during the Spanish-American War.
- Confirmed the theory that yellow fever is transmitted by a particular mosquito and not direct contact.
- His research greatly expanded the fields of epidemiology and Preventive Medicine and was essential for the completion of the Panama Canal.

WWI: Foundational Concepts

Hemorrhage Control

Blood Transfusion

Callum JL, Pinkerton PH. Transfusion. 2018 Nov;58(11):2476-2477.

Oswald Robertson

- English-American physician, 1886-1966
- Worked on blood typing & storage (1915)
- Deployed to France w/ Harvard 1917
- 1st blood bank, universal donor blood, ice box, stored in citrate/glucose

TRANSFUSION WITH PRESERVED RED BLOOD CELLS.

BY

OSWALD H. ROBERTSON, CAPT. M.O.R.C., U.S.A.,

U.S. ARMY BASE HOSPITAL.

BMJ 1918

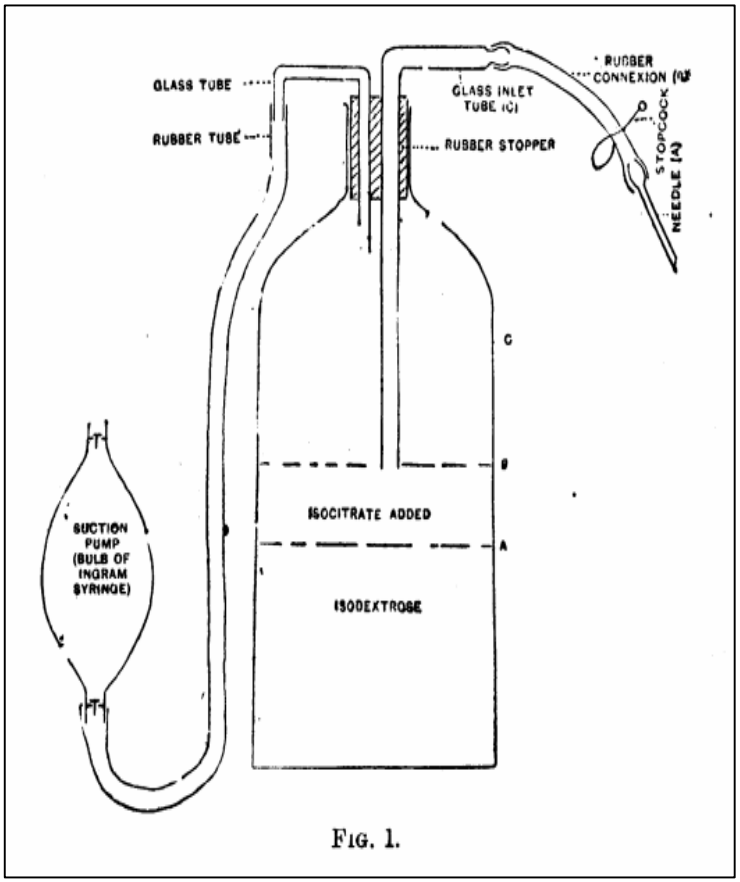
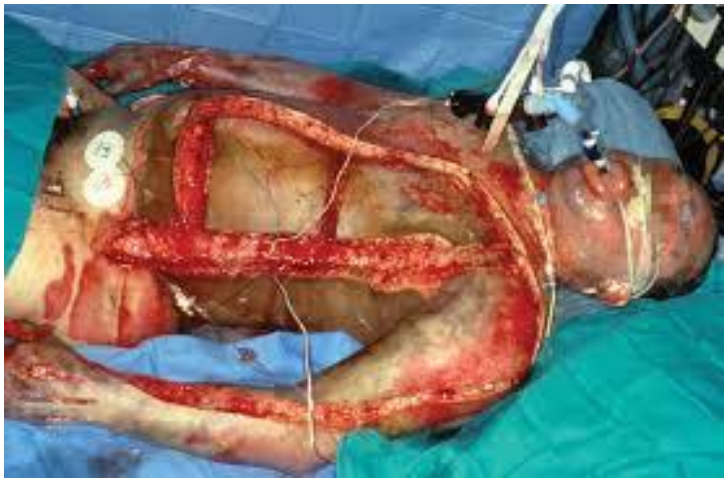


FIG. 1.

Transfusion bottle

Burns: A Terrible & Enduring Challenge



COL Basil Pruitt, MD (1930-2019)

- USAISR Commander, 1968-1996
- Developed modern burn shock resuscitation
- Introduced highly effective topical antibiotics in burn wound care
- Trained 46 burn unit directors, 23 department chairs, 11 past presidents ABA
- “Father” of modern burn care

US Army Institute of Surgical Research

Burn Center

*Sole DoD Burn Center
*1 of 70 ABA Verified
*Texas Regional Burn Center
* Second in the US/1949
*Leaders in burn research
* Burn Flight Team

Burn & Critical Care

Research

*Materiel solutions
*Knowledge products
*More effective combat casualty care
* Evidence-based
*Best clinical practice

Trauma & Burn Research

Readiness Training Platform

Operationally Responsive Clinical Research

Prolonged Field Care

Coagulation and Blood

Damage Control Resuscitation

Orthopedic Trauma Research

Dental Craniofacial Trauma Research Directorate

Multi-Organ Support Technology

Medical Effects of Directed Energy

Tactical Combat Casualty Care

Combat Trauma & Burn Injury Research

Battlefield Pain Management

Sensory Trauma

Center for Human Integrative Physiology

Clinical Research Support & Automation Research Branch

Clinical Research Support Branch

Optimizing Combat Casualty Care

US Army Institute of Surgical Research
Selected Recent Contributions (2001-2019)

Hemostatic Dressings

TXA

CAT Tourniquet

LTOWB

Cold Platelets

French FDP

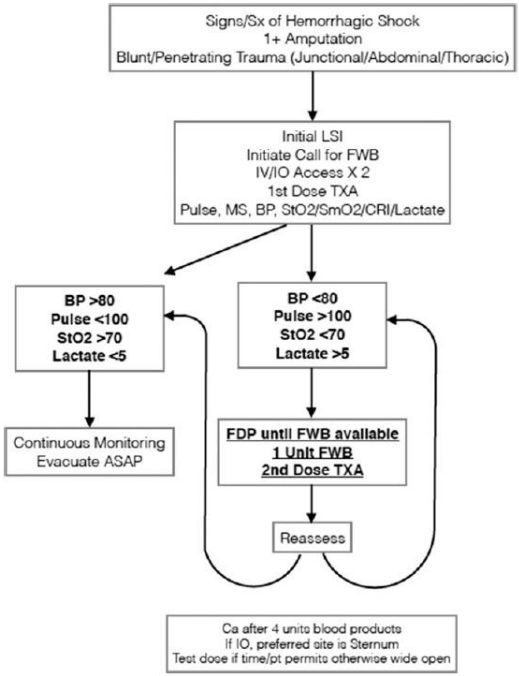


FIGURE 1. 75th Hemorrhagic shock.

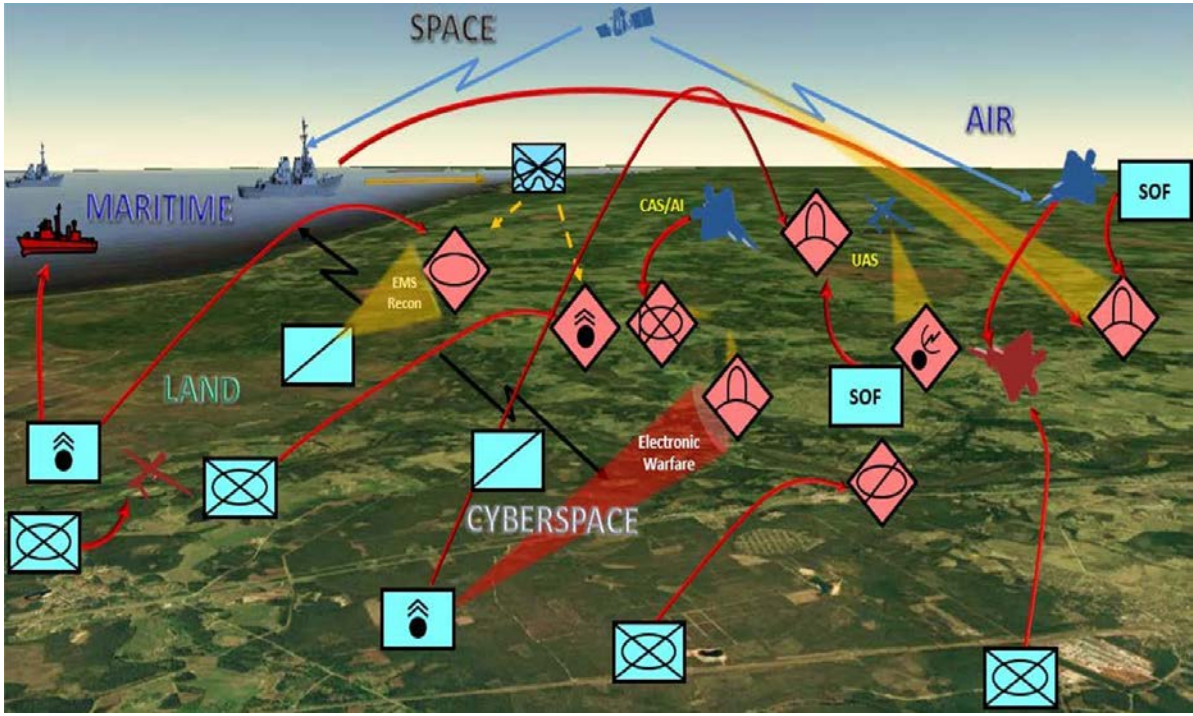
ROLO Protocol

“He who would become a surgeon should join an army and follow it.”

Hippocrates

New Operational Setting…
Multi-Domain Operations

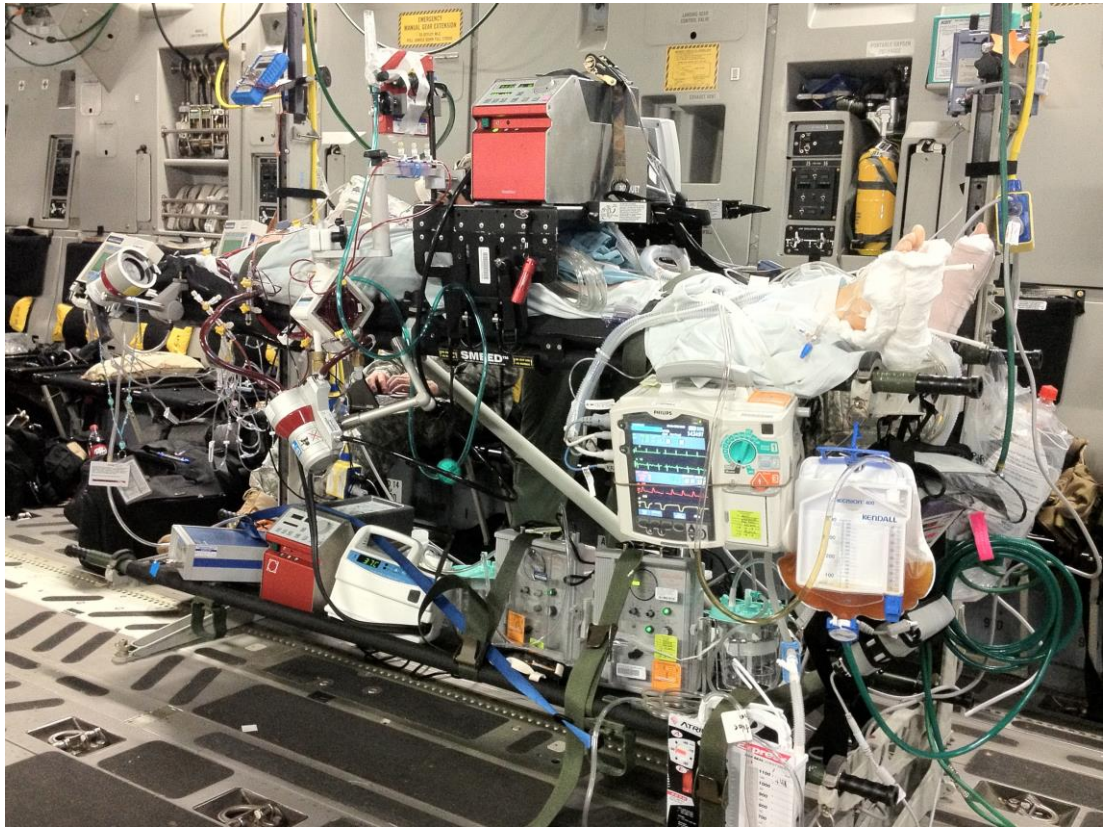
Remote, austere settings or dense urban environments…



delivering combat casualty care is getting more complicated!

Future Conflicts: More Sophisticated & Lethal Enemy Forces

Imperatives for the Future Battlefield: Simplify, Miniaturize, and Automate



Advanced Technology Solutions

Medical Robotics

Aerial Reconfigurable Embedded System (ARES)

Distribution Statement "A" (Approved for Public Release, Distribution Unlimited)

Artist Concepts

Questions?

“For Combat Wounded”

U.S. Army Institute of Surgical Research

Cooperative Research & Development Agreements (CRADA)

Robert (Bob) Charles, JD, LLM, MPH

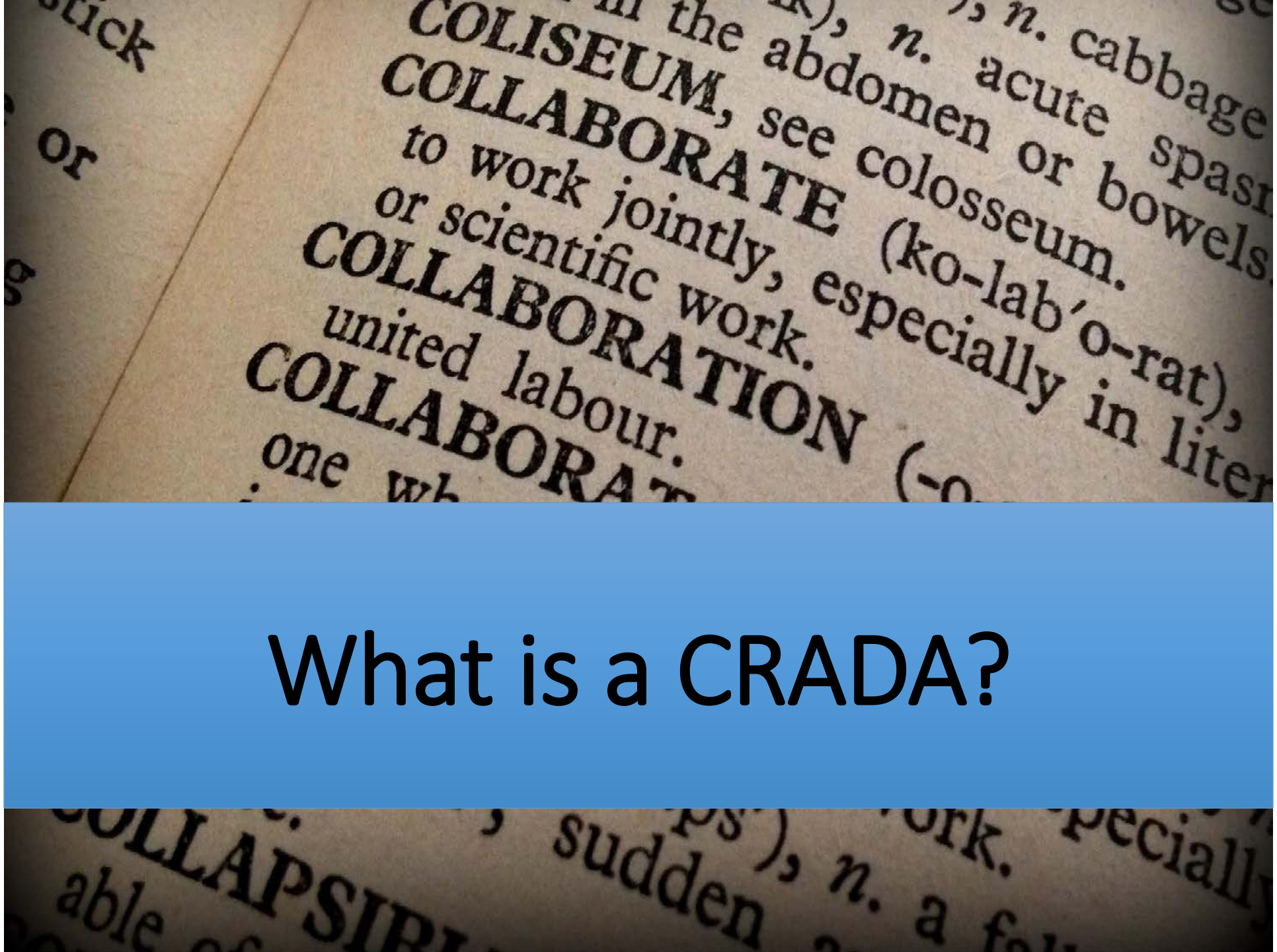
Army Medical Research and Materiel Command
Fort Detrick, Maryland
(301) 619-7663
robert.l.charles4.civ@mail.mil

Disclaimer

The opinions expressed by Mr. Charles during this presentation are his own and do not represent the position of the U.S. Government, the U.S. Department of Defense, the U.S. Army, Mrs. Charles, the Charles children, or grandchildren

Federal Technology Transfer

www.youtube.com/watch?v=KrhpLt0-auw&feature=youtu.be



What is a CRADA?

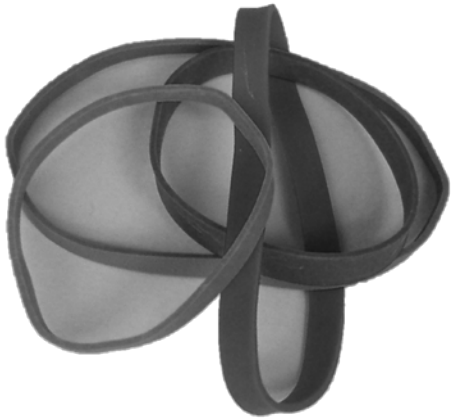
CRADA SUCCESS STORY

WaterStep

https://www.youtube.com/watch?v=Db9M1Si0Jkk

The Big Picture – a CRADA is:

- A kind of **government contract** allowing **R&D collaborations** between federal labs & nonfederal parties



Allows labs great flexibility/discretion

Enables transfer of resources to and from federal govt

Legal Definition

“. . .any agreement between one or more Federal laboratories and one or more non-Federal parties under which the Government, through its laboratories, provides personnel, services, facilities, equipment, intellectual property, or other resources, with or without reimbursement (but not funds to the non-Federal parties) and the non-Federal parties provide funds, personnel, services, facilities, equipment, intellectual property, or other resources toward the conduct of specified research and development efforts which are consistent with the missions of the laboratory;”

—15 USC §3710a(d)(1)

"…***the Government***, through its laboratories, ***provides personnel***…"

Example:

The federal lab sends an engineer and a technician to the CRADA partner's facility for two weeks to carry out tests and evaluation of the partner's technology using both parties' unique testing equipment.

"…***the Government***, through its laboratories, ***provides***… ***facilities***…"

Example:

The Nonfederal party is allowed to use an otherwise empty facility on a federal installation near the laboratory for one year to carry out CRADA activities.

"…***the Government***, through its laboratories, ***provides*** … ***equipment***…"

Example:

The federal lab loans a specialized microscope to the partner's for 6 months to carry out part of the effort under the CRADA.

"…***the Government***, through its laboratories, ***provides***… ***intellectual property***…"

Example:

The federal lab grants the partner a nonexclusive license to use a lab's patented invention for three years to carry out CRADA research and to develop other specified commercial technology. The CRADA partner pays the lab $10,000 for the license.

"…***the Government***, through its laboratories, ***provides*** (these resources) ***with or without reimbursement***…"

This is stand-alone, discretionary to the lab, statutory authority to negotiate and receive reimbursement from $0.00 up to fair market value for whatever the lab will provide or has provided

"…***the Government***, through its laboratories, ***provides*** personnel, services, facilities, equipment, intellectual property, or other resources with or without reimbursement ***(but not funds to the non-Federal parties)***…"

The lab cannot provide funds, but it can direct the partner to other potential funding sources, such as grants, SBIR, state economic development funds, etc.

(but not funds to the non-Federal parties)…"

- "Relationship to other laws - Nothing in this section is intended to limit or diminish existing authorities of any agency."
  15 USC 3710a(f)

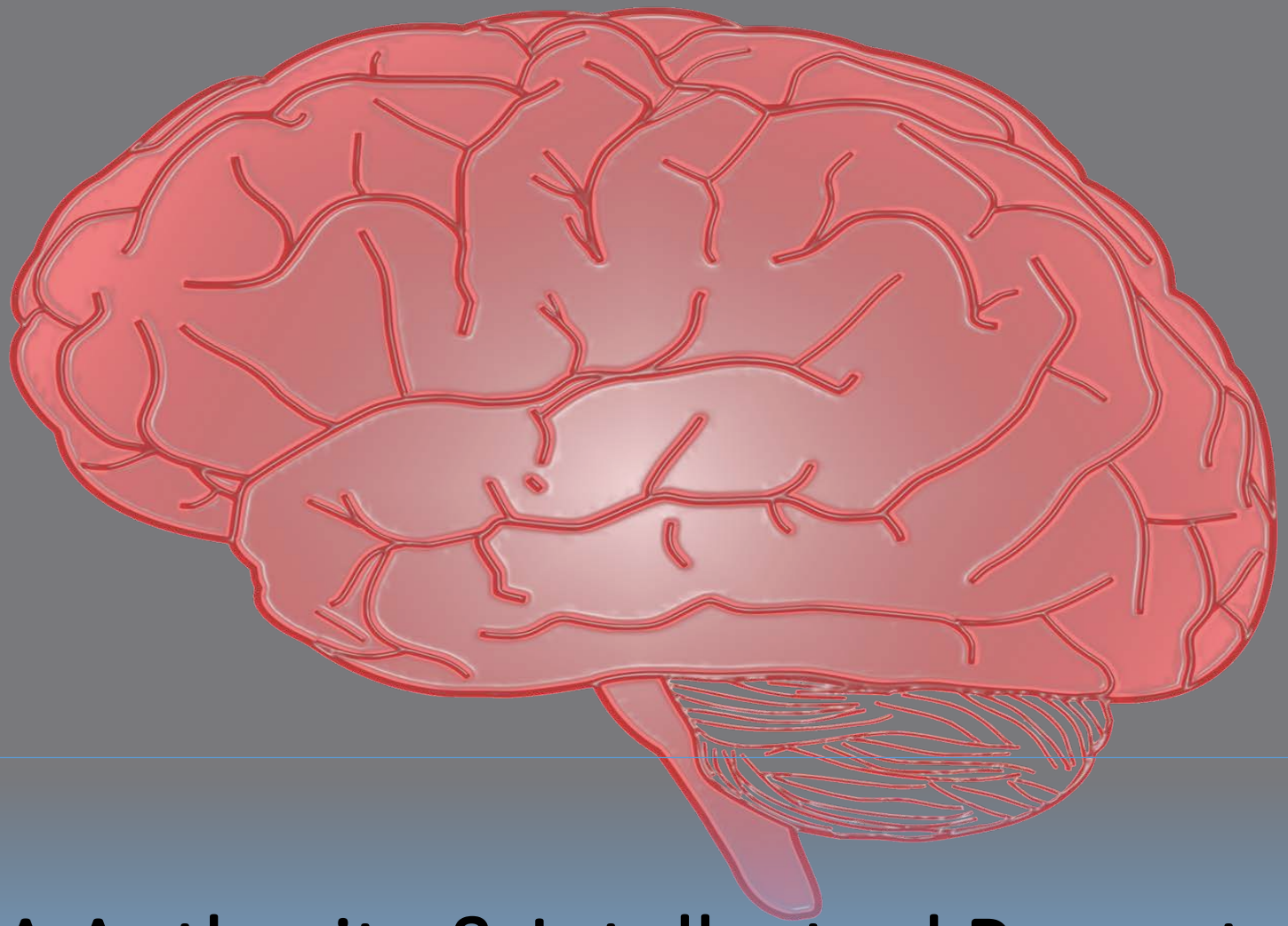
- "Nevertheless, this section is not intended to prohibit Federal financial contributions as might be authorized and appropriated by other acts of Congress."
  Senate Report 99-293, April 21, 1986

- Agencies can award contract, grant, cooperative agreement, or STTR funding to a CRADA collaborator, which can then, in turn, provide those funds to a federal lab under a CRADA
  (e.g., FR/Vol. 70, No. 241, Friday, Dec. 16, 2005/Notices, page 74937, paragraph 9(c)(2)(i)-(iii); Assistance/Procurement Advisory Notice 15-01, U.S. Army Medical Research Acquisition Activity)

"…any agreement between one or more Federal laboratories and one or more non-Federal parties under which… ***the non-Federal parties provide funds, personnel, services, facilities, equipment, intellectual property, or other resources…***"

All resources to be provided by the parties, including how much reimbursement goes to the lab, are

https://www.youtube.com/watch?v=oFlsjK-R8hU



CRADA Authority & Intellectual Property

CRADA Authority

"Each Federal agency ***may*** permit the ***director*** of any of its Government-operated Federal laboratories…

"(2) to ***negotiate licensing agreements*** under section 207 of title 35 . . . ***for inventions made or other intellectual property developed at the laboratory*** and other inventions or other property that may be voluntarily assigned to the Government."
—15 USC 3710a(a)(2)

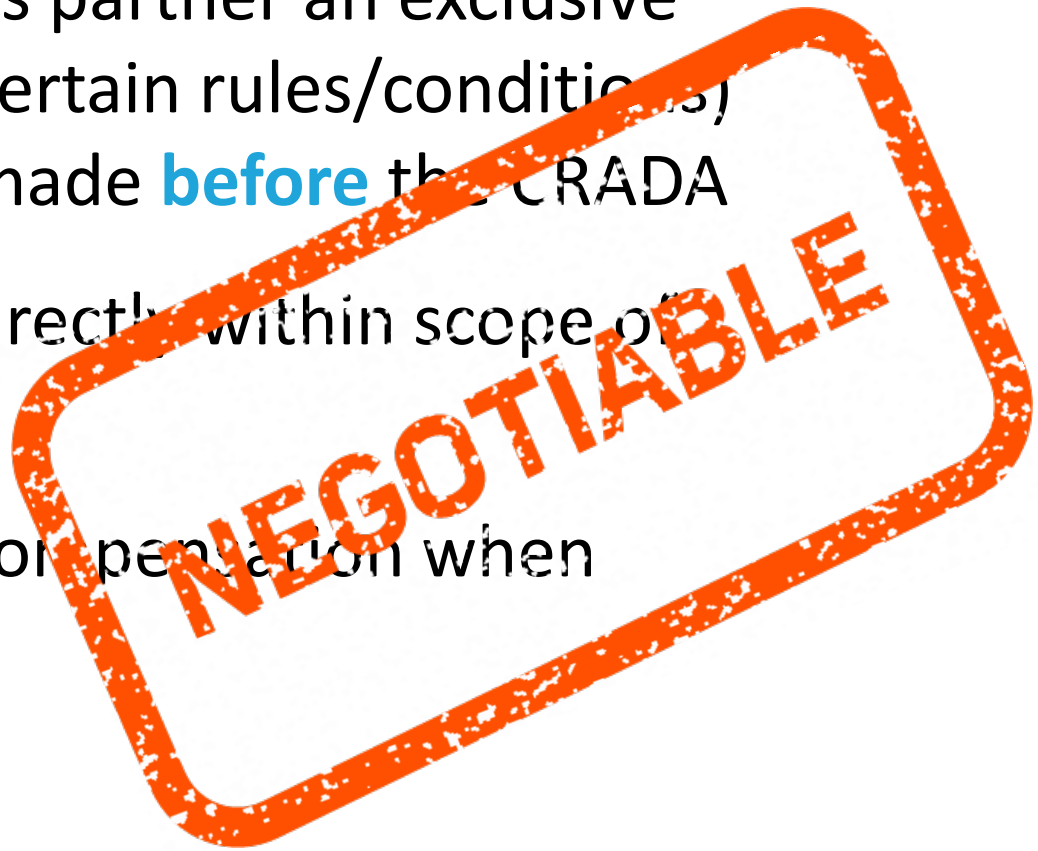
- Covers inventions made **under CRADAs or otherwise**

CRADA Authority (15 USC 3710a(b))

Lab shall ensure that CRADA partner(s) has an option to choose an exclusive license **for a pre-negotiated field of use**

Granting Exclusivity

- The lab may grant its partner an exclusive license (subject to certain rules/conditions) for a lab invention made **before** the CRADA
  - If the patent is directly within scope of the CRADA
  - For reasonable compensation when appropriate



Labs may **waive**, in advance, any government ownership rights to joint CRADA subject inventions subject to the reservation of a nonexclusive license

—15 USC 3710a(b)(3)(D)

https://www.youtube.com/watch?v=BYO6e9UH-6Q

Lab Director Responsibilities

Must give:

- "Special consideration" to **small businesses** and small business consortia

- "Preference" to **U.S. businesses** that agree to "manufacture substantially" in the U.S.

—15 USC 3710a(c)(4)

Miscellaneous Issues

No Competition Required!

Data Rights

CRADA Format

- Substance is much more important

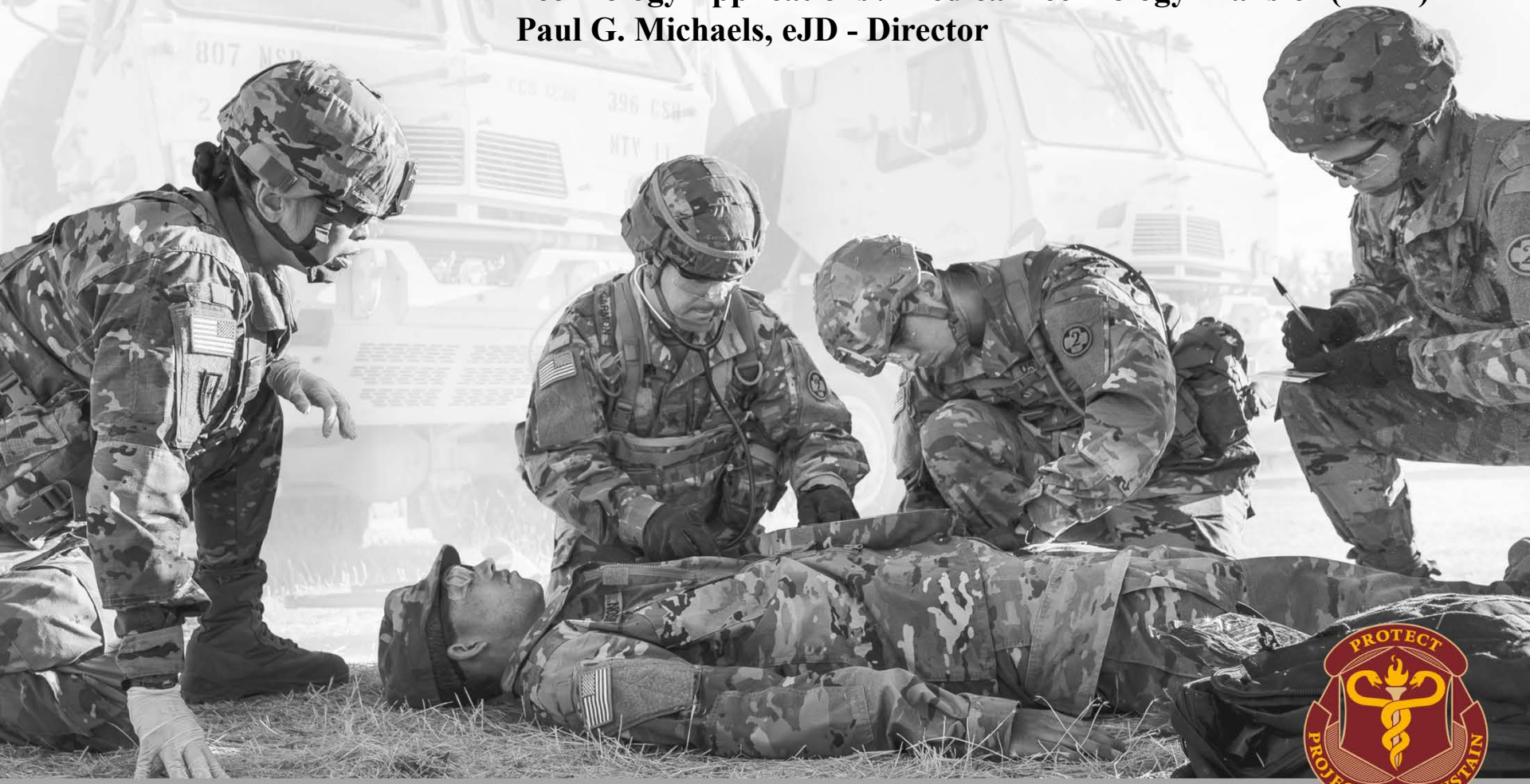
Statement of Work (SOW)

- Can include
  - Milestones
  - Go/no-go decisions
- Can be **renegotiated** as circumstances change

Questions?

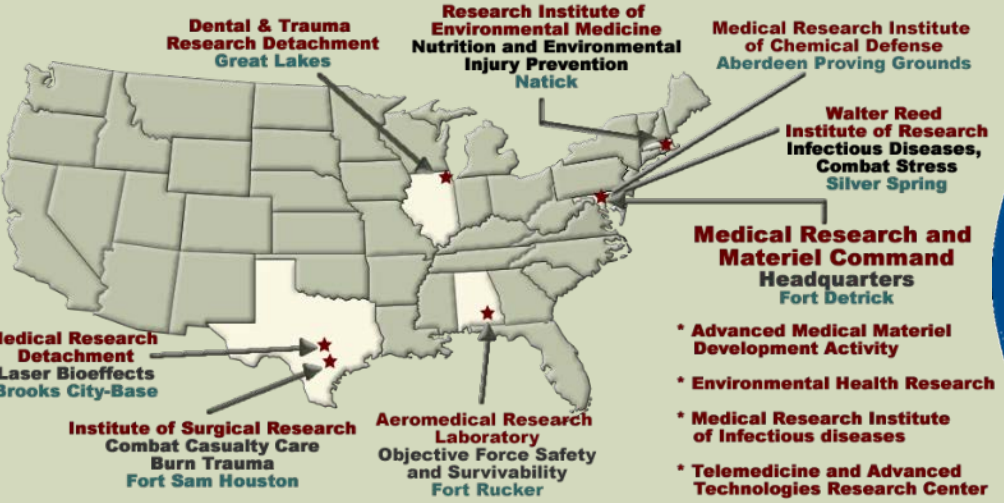
U.S. Army Medical Research and Materiel Command

MRMC - Office of Research and Technology Applications / Medical Technology Transfer (MTT)
Paul G. Michaels, eJD - Director



US Army Medical Research and Materiel Command

- Headquartered at Fort Detrick, MD
- The Medical R&D arm of the Army
- Army's medical materiel developer
- $2.5 billion RDT&E funding in FY 2017
- >6500 personnel worldwide



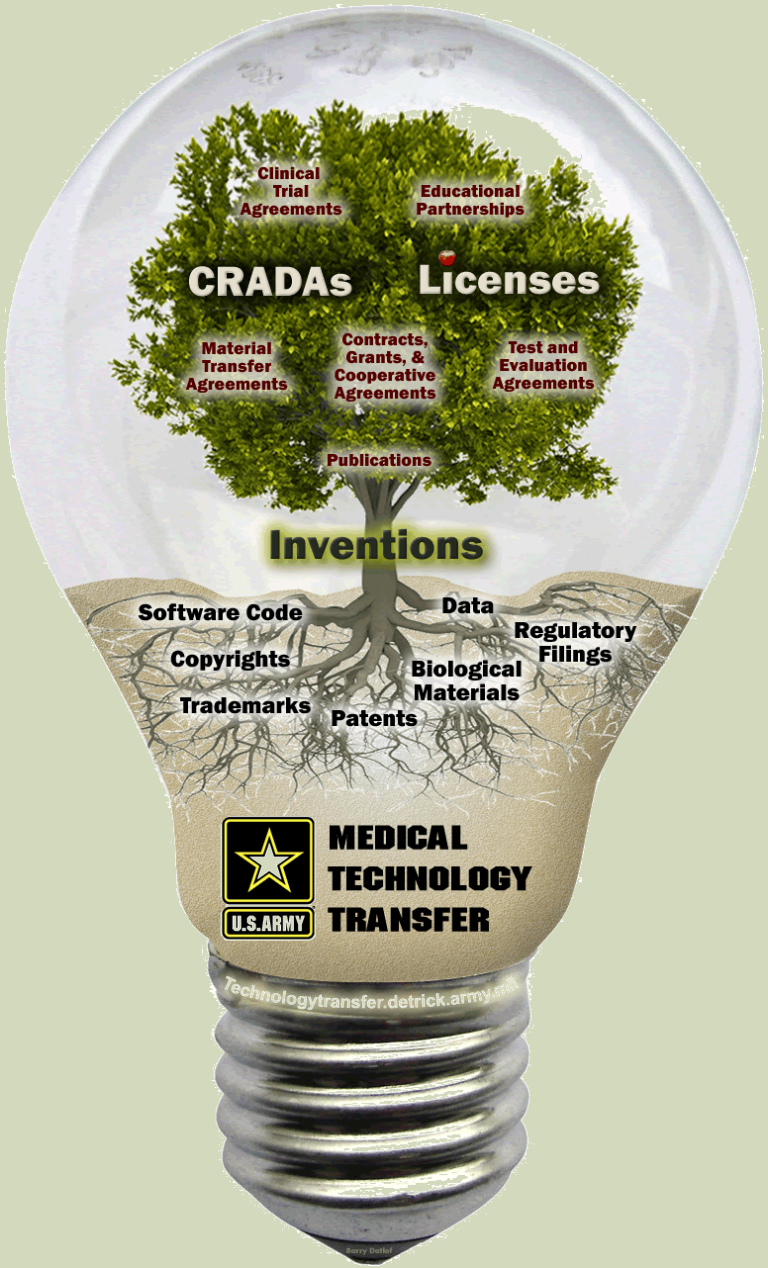
TECHNOLOGY TRANSFER FACILITATES R&D PARTNERING AND COMMERCIALIZATION

Technology Transfer

is the exchange of knowledge and materials among parties for the development and utilization of new products and services

Keys laws driving Technology Transfer

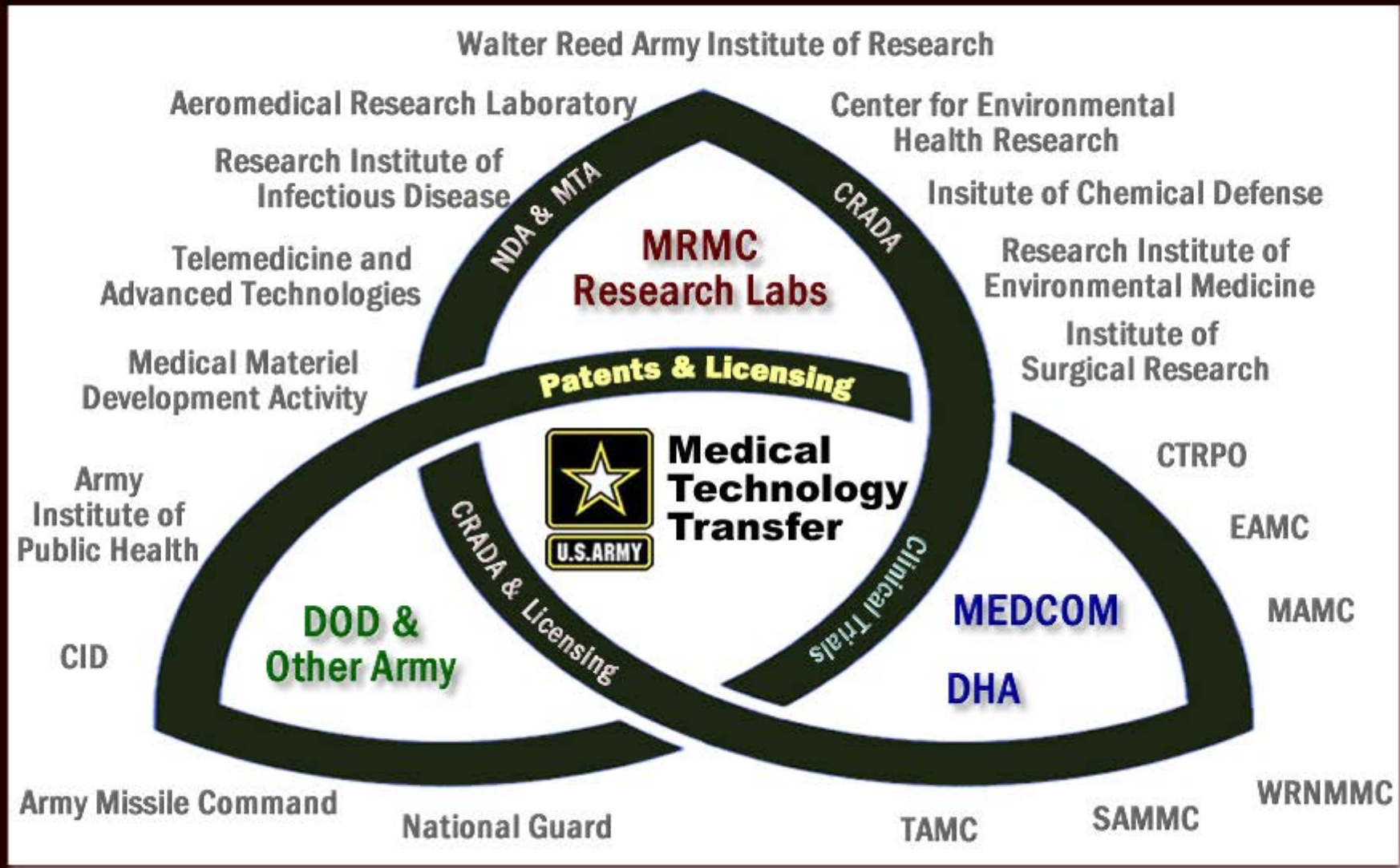
- Stevenson-Wydler Technology Innovation Act of 1980
- Bayh-Dole Act of 1980
- Fed Technology Transfer Act of 1986



Currently:
82 Licenses
25 Products in the Market Place

Key Daily Issues:
Discoveries, Inventions, Novelty, Invention Disclosures, Docketing, Invention Evaluation Committee (IEC) Meetings, Patent Applications US/Foreign, Licensing, Royalties, Collections, Distributions, Handling Infringement (DOJ), Enforcement (DOJ), Auditing, Payment Plans, Terminations, and Close Out.

Medical Technology Transfer Nexus Model

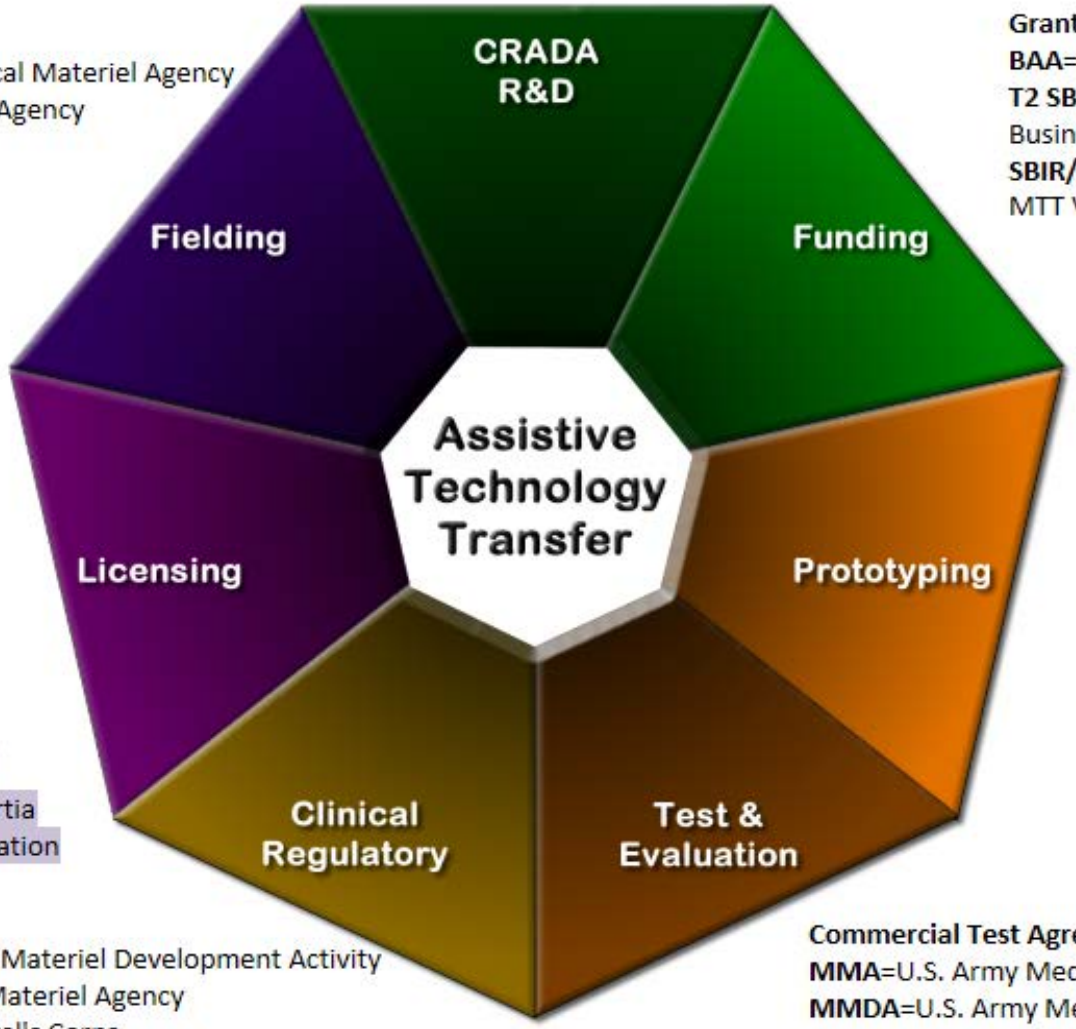


Assistive Technology Transfer is a Life Cycle

Lab and/or Third Party Research and Development

MMA=U.S. Army Medical Materiel Agency
DLA=Defense Logistics Agency

Grants and contracts,
BAA=Broad Agency Announcements,
T2 SBIR=Technology Transfer Small Business Innovation Research,
SBIR/STTR, Royalty income seed,
MTT Venture Fund (future)



Patents,
Copyrights,
Trademarks,
Materials,
Software, and
Know how Licenses

Purple Book,
Spinouts, Awards,
Media, Tradeshows,
Entrepreneur Sabbatical,
Media, TechLink, Startups,
International Patent Consortia
and Minerva Inventor Education

MMDA=U.S. Army Medical Materiel Development Activity

ECBC=Edgewood Chemical Biological Center

MTEC=Medical Technology Enterprise Consortium

MMDA=U.S. Army Medical Materiel Development Activity
MMA=U.S. Army Medical Materiel Agency
JAG=Judge Advocate General's Corps
AMEDDC&S= Army Medical Department Center and School

Commercial Test Agreements,
MMA=U.S. Army Medical Materiel Agency
MMDA=U.S. Army Medical Materiel Development Activity
AARL=U.S. Army Aeromedical Research Laboratory
AFMESA=Air Force Medical Evaluation Support Activity

U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND

MEDICAL TECHNOLOGY TRANSFER

RESEARCH
DEVELOPMENT
PRODUCTS

Last Modified Date: 01 Dec 2017

Printer Friendly | Download Adobe Reader | A A A

- About Medical Technology Transfer
- Technologies Available for Licensing
- Templates and Forms
- Upcoming Events
- Awards and Recognition
- Policy (External PDF)
- Frequently Asked Questions
- Links and Resources
- Contact Us

USAMRMC Informational Marketing Material

- Products Portfolio (PDF 37.4 MB)

Home › About Medical Technology Transfer

About Medical Technology Transfer

What We Do

We provide **Assistive Technology Transfer (AT2)** to industrial and academic partners to speed the development and commercialization of DOD-relevant biomedical inventions. AT2 mechanisms include: assisting in the identification, contracting, and execution of R&D, Funding, Prototyping, Test & Evaluation, Clinical/Regulatory Affairs, Licensing, and Fielding.

10 Things to Know for a Collaboration

Our primary mission is to license new and improved biomedical technologies for the benefit of the warfighter.

Have a smart idea about how to advance any of our discoveries?

Here are 10 things you need to know to develop a collaboration:

1. **Non-Disclosure Agreements (NDA)** – Used for the sharing of "Proprietary Information" between MRMC and an outside party.
2. **Cooperative Research and Development Agreements (CRADA)** – Used for MRMC to perform collaborative R&D with academic, industrial, not for profit, and nonfederal government parties. MRMC can provide materials, equipment, access to facilities, expertise, but not money to the CRADA partner (CRADA partner can provide the same plus funding to MRMC). CRADA partners receive a time-limited option to take an exclusive license to Government rights in CRADA-subject inventions within the field of the CRADA.
3. **License Agreements** – Used for the transfer of Intellectual Property from MRMC to a commercial

technologytransfer.amedd.army.mil

3. **License Agreements** – Used for the transfer of Intellectual Property from MRMC to a commercial partner. Noncommercial CRADA and IIA partners may also be granted licenses by MRMC, as long as they then sublicense to a commercial partner. Commercial Evaluation Licenses are given for short term evaluation of the commercial potential of an MRMC invention.

What is Licensed:	Patents, Copyrights, Trademarks (directly licensed by Army Trademark Licensing Program), and Other Intellectual Property
Types of Exclusivity:	Exclusive*, Partially Exclusive*, or Nonexclusive (*requires Federal Register announcement)
Fields of Use:	May be topical (e.g. therapeutic vs. diagnostic), geographical (e.g. US vs. worldwide), or how the invention is used (production vs. testing vs. sales/distribution)
Rights to Sublicense:	May be granted with written approval of MRMC

4. **Commercial Test Agreements (CTA)** – Used for MRMC to test materials, equipment, models, computer software, and other technologies on behalf of an outside party. Partner owns the technical data and any intellectual property that may arise from the testing.
5. **Interinstitutional Agreements (IIA)** – Used for R&D collaborations or licensing among 2 or more Federal agencies. Stipulates which agency does what and with which funds and how deployment and commercialization will be done.
6. **Partnership Intermediary Agreements (PIA)** – Used for promoting cooperative activities between MRMC and a State or local government (or a nonprofit operating on behalf of a State or local government). It facilitates the transfer of technology for the benefit or economic development of a State or local government, small business, or educational institutions; and supports the mission of MRMC.
7. **Contracts** – Used for MRMC funding of R&D by outside parties; Government retains Government use rights for federally funded inventions, but Contractor may retain ownership and commercialize inventions created under the contract.
8. **Grants** – Used for MRMC funding of R&D in academia, industry, and not for profits (does not use MRMC Resources). Grant recipient may elect title to and commercialize new inventions create under the grant.
9. **Cooperative Agreements** – Used for MRMC funding of R&D in academia, industry, and not for profits (that also uses MRMC Resources).
10. **Other Transaction Agreements (OTA)** – Use for MRMC participation in prototyping collaborations with industry.

MTT Website Lists Available Inventions for Commercialization

Home › Technologies Available for Licensing

Technologies Available for Licensing

For Licensing Opportunities, please contact the ORTA at USArmy.Detrick.MEDCOM-USAMRMC.List.ORTA@mail.mil

Available Patents: RSS feed

Search for technologies: Search

Displaying up to 10 patents per category, with no filters.
Show all patents

Jump to: Antibody Technologies | Assay | Design | Device | Diagnostic | Method | System | Therapeutic | Treatment | Vaccine

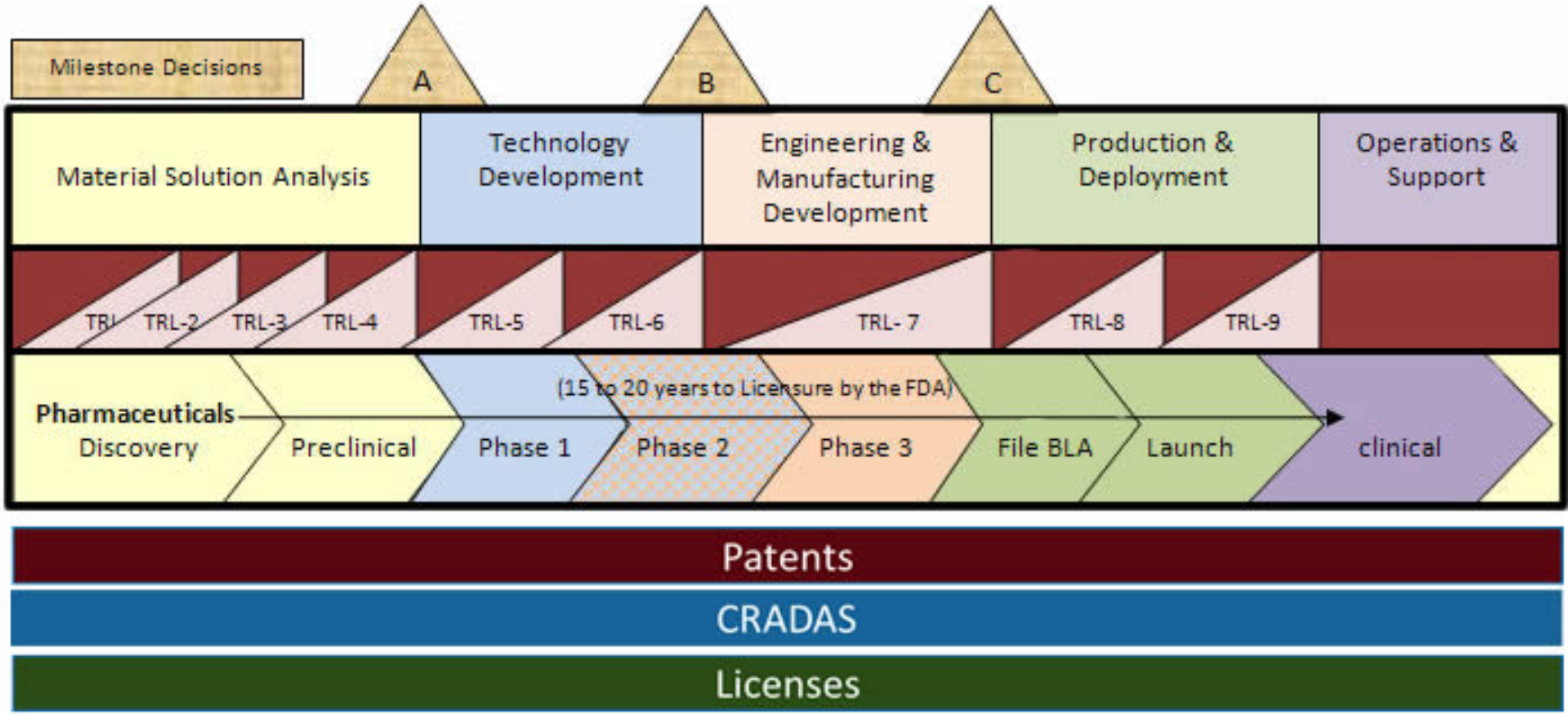
Antibody Technologies

Show 10 entries Search:

Published/ Issued No.	Published/ Issued Date	Title	Lab	Abstract	Inventors
10,160,795	12/25/18	NEUTRALIZING ANTIBODIES TO EBOLA VIRUS GLYCOPROTEIN AND THEIR USE	RIID		SULLIVAN (TREFRY)
10,081,669	09/25/18	THERAPY FOR FILOVIRUS INFECTION	RIID		LAI (DYE), ET AL
10,064,858	09/04/18	METHODS AND COMPOSITIONS FOR TREATING BACTERIAL INFECTIONS WITH IRON CHELATORS	WRAIR		ZURAWSKI
9,346,875	05/24/16	THERAPY FOR FILOVIRUS INFECTION	RIID		DYE, JOHN
9,193,739	11/24/15	INDUCTION OF HIGHLY SPECIFIC ANTIBODIES TO A HAPTEN BUT NOT TO A CARRIER PEPTIDE BY IMMUNIZATION	WRAIR		ALVING, ET AL
9,119,828	09/01/15	ANTIBODIES WITH SIMULTANEOUS SUBSITE SPECIFICITIES TO PROTEIN AND LIPID EPITOPES	WRAIR		ALVING, CARL
8,778,889	07/15/14	ANTIMICROBIAL DECAPEPTIDE ORAL HYGIENE TREATMENT	WRAIR		LEUNG, KAI
7,879,330	02/01/11	ANTIBODIES AGAINST TYPE A BOTULINUM NEUROTOXIN	RIID		BAVARI, S.; TORRES-MELENDEZ, E.; LEBEDA, F.
7,795,015	09/14/10	ANTIBODIES EXPRESSED IN INSECT CELLS	RIID		GUTTIERI, M.; SCHMALJOHN, C.
7,563,875	07/21/09	RECOMBINANT CHIMERIC HUMAN ANTI-BOTULINUM	RIID		PALYS, T.; SCHOEPP, R.;

Over 448 technologies!

Understanding your TRL (Technology Readiness Level) is important

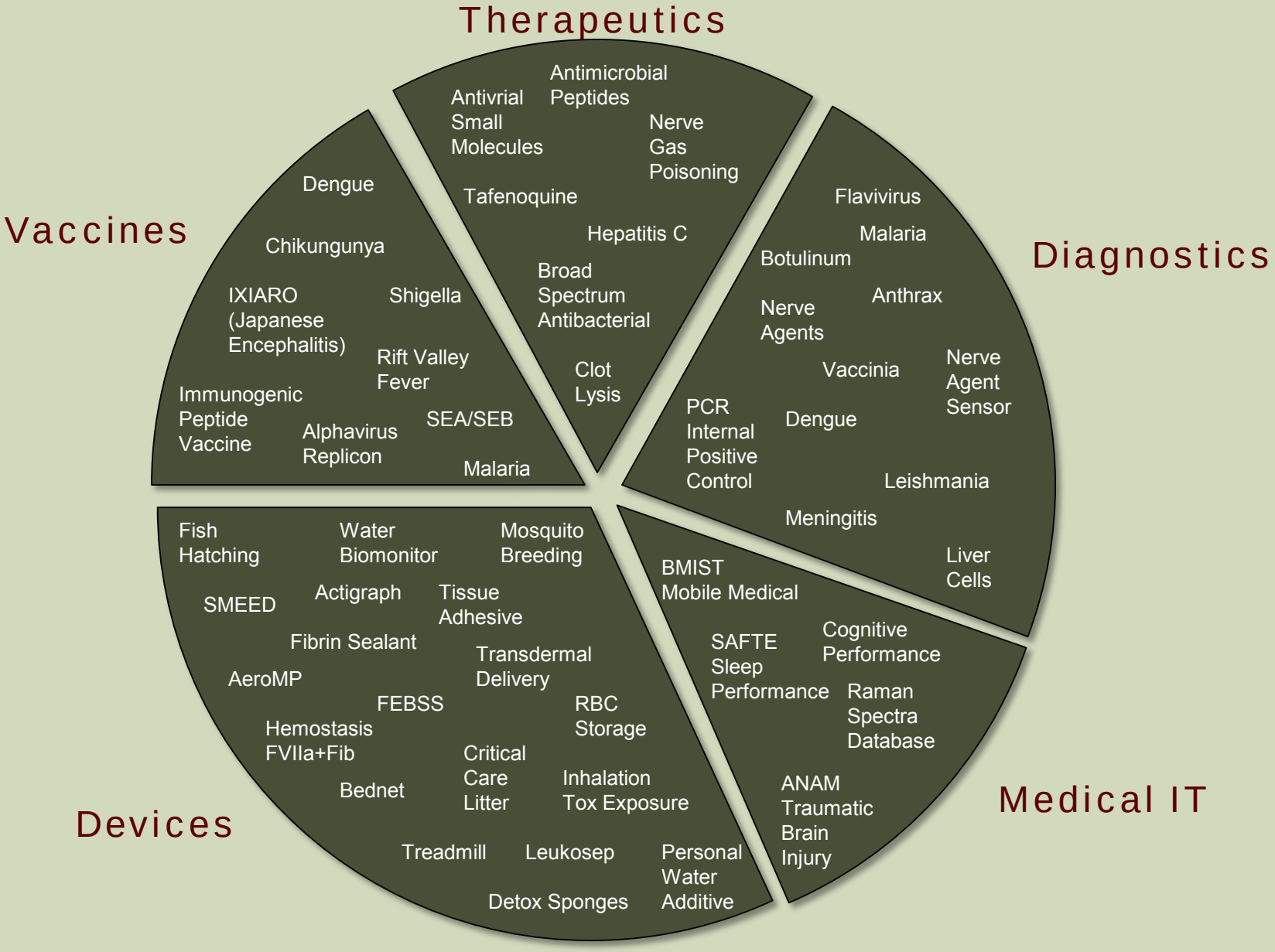


Focused on the Warfighter
Technology Out of the Commands and Into the Hands of the User in the Shortest Time

- Combat Casualty Care
- Military Operational Medicine
- Infectious Diseases
- Medical Chemical Defense
- Medical Biological Defense
- Medical Logistics
- Medical IM/IT
- Medical Facilities Planning

Vaccines | Diagnostics | Therapeutics | Medical Devices | Medical IT

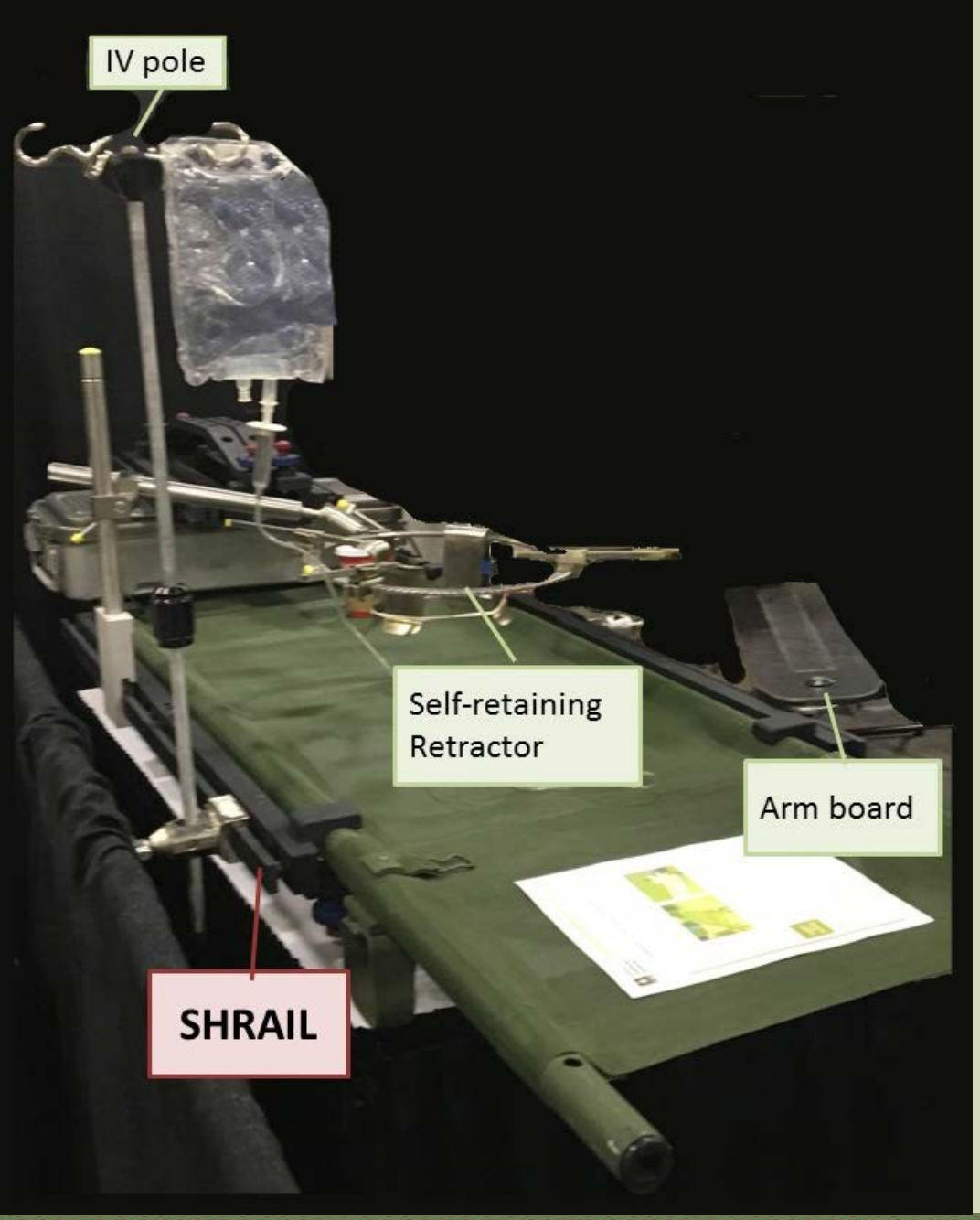
Licensing Moves A Variety of Products Toward Commercialization



MRMC Product Successes

Vaccines:

- Hepatitis A
- Meningococcal Tetravalent
- Japanese Encephalitis
- BioThrax Anthrax

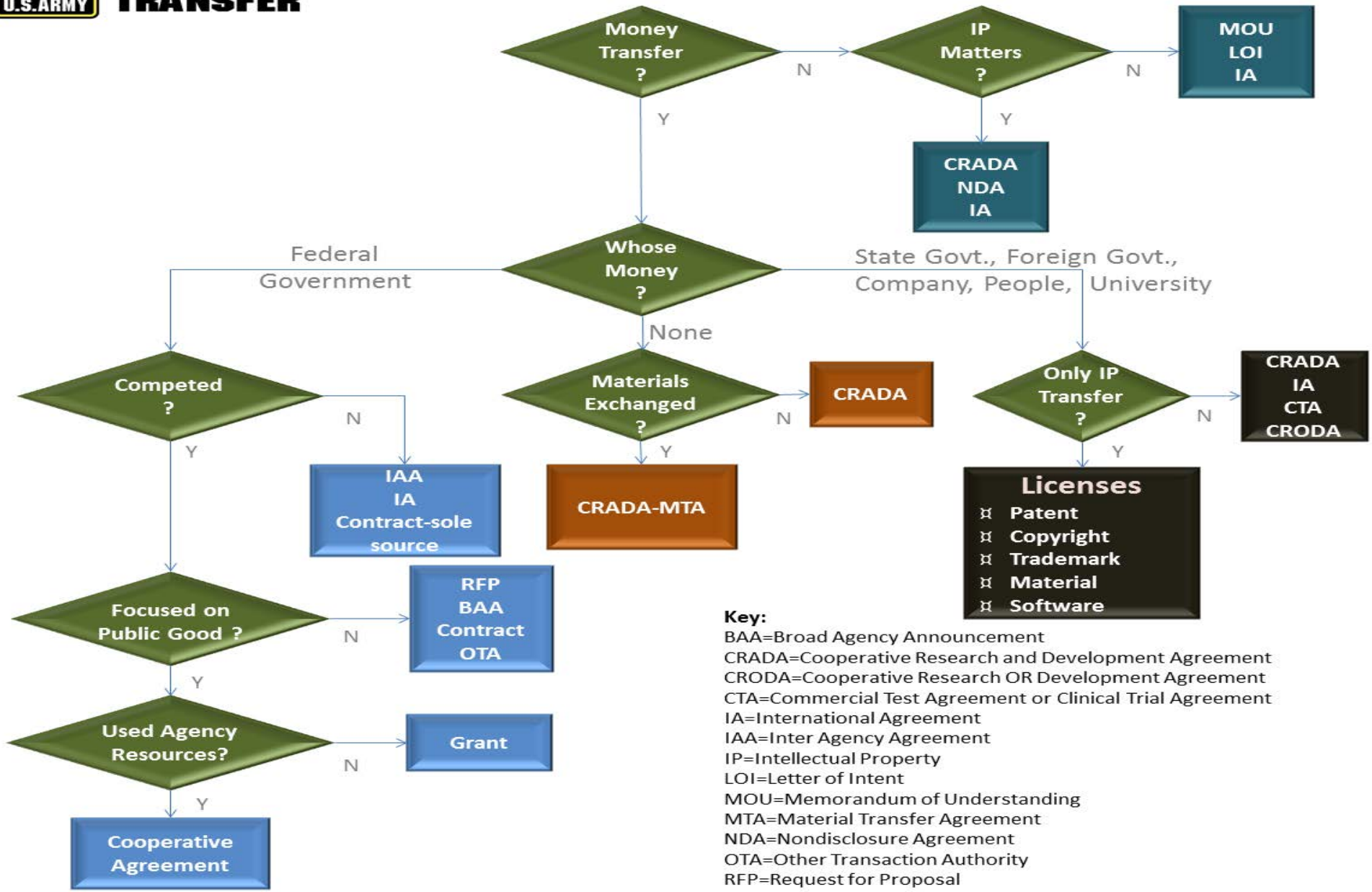


Attaching standard operating room devices to a field litter and allowing them to stay with the patient during transport is needed

MEDICAL TECHNOLOGY TRANSFER

U.S.ARMY

T2 Agreement Selector



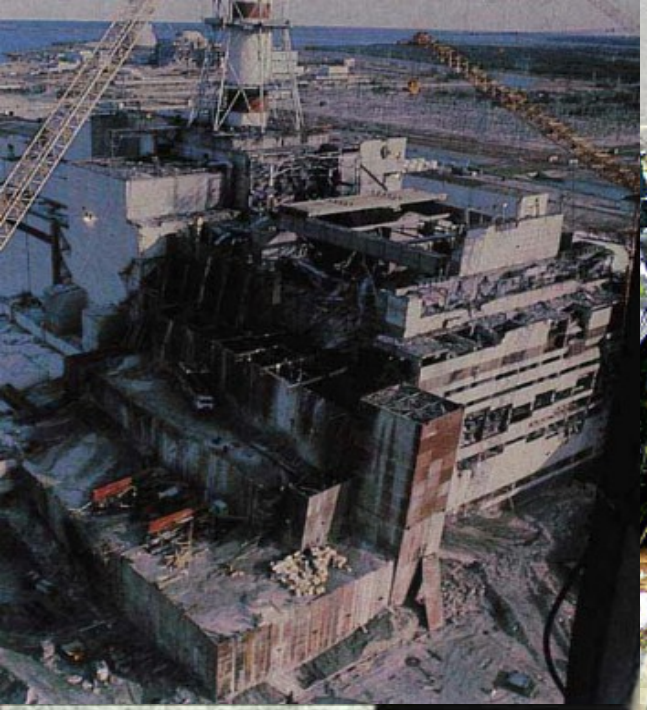
Key:

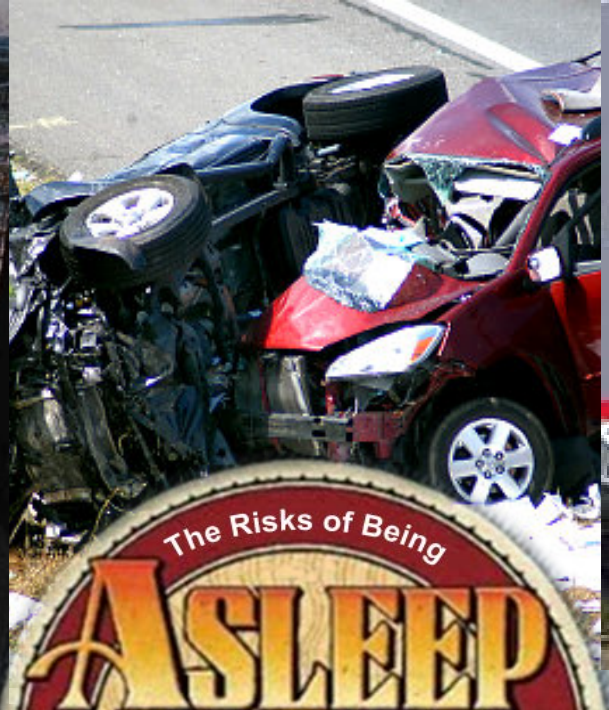
BAA=Broad Agency Announcement
CRADA=Cooperative Research and Development Agreement
CRODA=Cooperative Research OR Development Agreement
CTA=Commercial Test Agreement or Clinical Trial Agreement
IA=International Agreement
IAA=Inter Agency Agreement
IP=Intellectual Property
LOI=Letter of Intent
MOU=Memorandum of Understanding
MTA=Material Transfer Agreement
NDA=Nondisclosure Agreement
OTA=Other Transaction Authority
RFP=Request for Proposal

Additional Information: *technologytransfer.detrick.army.mil*

Copyright 2016 U.S. Army Medical Research and Materiel Command

Disclaimer: Since we could never find 2 lawyers to concur on every item, use in good health and at your own risk

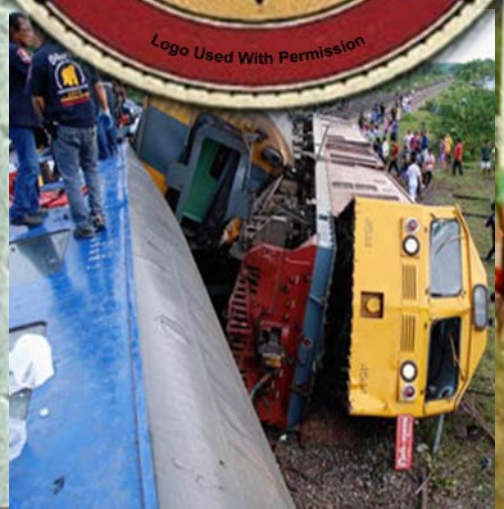




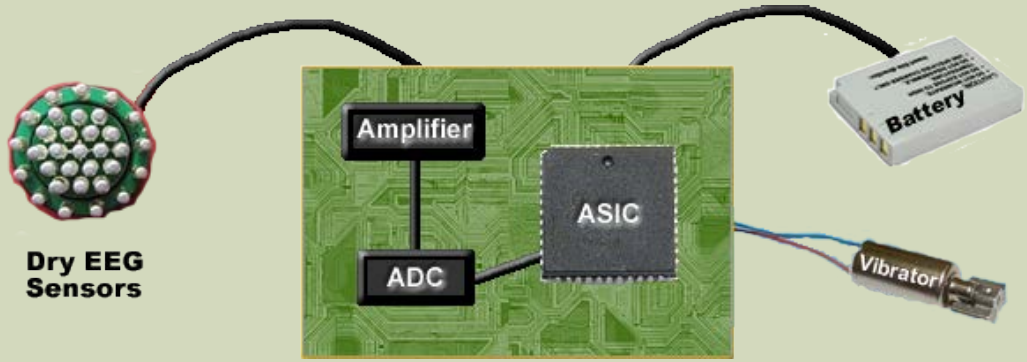
The Risks of Being

ASLEEP AT THE WHEEL

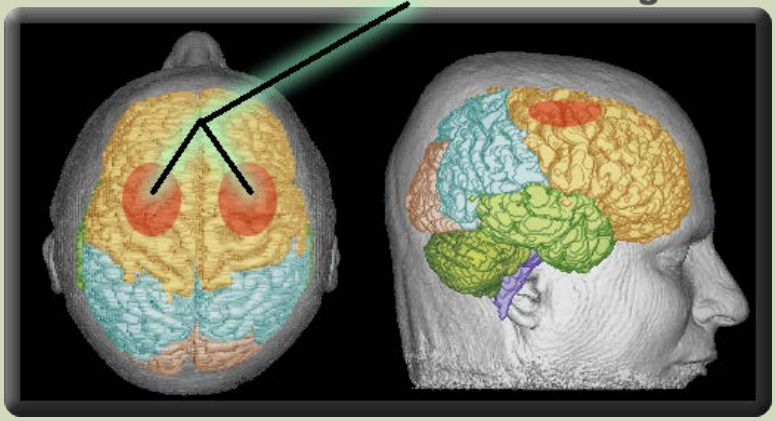
Logo Used With Permission



License It: AlertCap™ Continuously Monitors EEG Brain Waves and Immediately Sounds An Alarm Before You Lose More Alertness



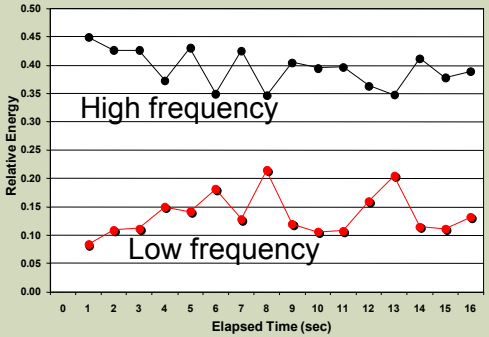
EEG Monitors the C3/C4 Brain Regions



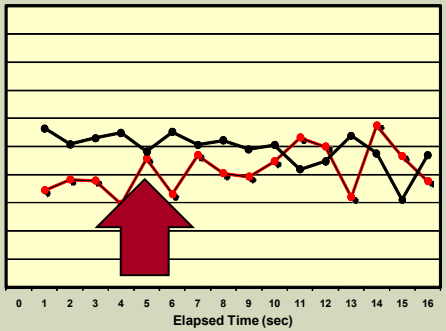
Patent Status:
U.S. Patent 8,285,372

High and Low Frequency EEG Bands

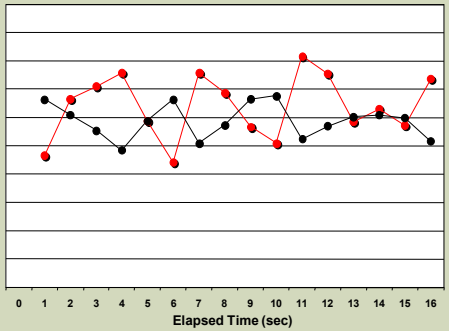
Awake



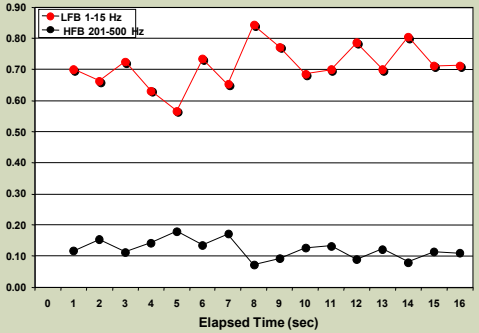
Neutral



Drowsy



Asleep



AlertCap™ Buzz

Head Nodding

Eyelid Closing

Slower
Reactive
Costlier & more complicated

Startup Financing and the Valley of Death

Public Financing

Founders, Friends & Family

Crowd Sourcing

Loans

MRMC

SBIR
STTR
BAA
AAMTI
CDMRP
CRADA
FDBDO

Maryland

- TEDCO
- Seed Funding Program
- Mtech
- MIPS
- Others

MRMC + Maryland

Angel

Venture Capital

Bridge Capital

Joint Ventures

IPO

Follow On

Federal, State, and University Research Funding

Crowd Donations $10-50K

Angel Round $25-500K

Seed/Startup Round $.5-3M

A Round $2-10M

B Round $5-25M

C Round $50M+

Barry Datlof

Information

Paul Michaels, eJD
Director, ORTA

301-619-4145
Paul.G.Michaels.civ@mail.mil

technologytransfer.amedd.army.mil

Medical Technology Enterprise Consortium (MTEC)

ISR Industry Day

March 28, 2019

MTEC
Medical Technology
Enterprise Consortium

Bill Howell
Chief Operating Officer
William.Howell@tunnellgov.com
www.mtec-sc.org

MTEC
Medical Technology
Enterprise Consortium

MTEC Mission

"Protect and Heal Those Who Serve"

To **be the partner of choice** for private industry, academic institutions, government agencies, and other research organizations seeking to accelerate the development of medical solutions that **prevent and treat injuries**, and **restore America's military and veterans to full health.**

MTEC
Medical Technology
Enterprise Consortium

MTEC is a 501(c)(3) organization

- Awarded a 10 year, renewable contract in 2015 from U.S. Department of Defense (DoD)
- Funds biomedical research and prototyping focused on DoD medical R&D needs using a Prototype OTA
- Reduces the risk of prototype technologies so that industry will advance development and finalize technology into a marketable product
- Facilitates commercialization of Government intellectual property and follow-on production for the U.S. Army

MTEC
Medical Technology Enterprise Consortium

Definition of Prototype Project

According to the most recent DoD OT Guide for Prototype Projects:

- A prototype project can be a preliminary pilot, test, evaluation, demonstration or agile development activity.
  - It may include systems or subsystems, components or materials, methodology or processes and technology
  - It can be used to evaluate the feasibility of a particular technology, process, concept, end item, effect, or other discrete feature

- Prototype projects may involve proof of concept, pilot, novel application of a commercial technology for a defense application, and/or creation, design, development, demonstration of technical or operational utility as related to a prototype. For medical R&D a "prototype" could be:
  - a clinical trial to establish drug efficacy;
  - designing and prototyping a medical device;
  - developing a manufacturing procedure;
  - establishing QA/QC standards for a manufacturing process

- **Prototype projects are NOT: basic research, services, maintenance, production (including LRIP) and construction**

MTEC
Medical Technology
Enterprise Consortium

MTEC is Unique

- Unlike similar non-profits that attempt to accommodate warfighter functional handicaps, **MTEC is focused on preventing and treating injury, and restoring lost or impaired function**

- Represents a **"first of its kind"** construct that **combines the "traditional" Government-funded project work with requirements to raise and execute private sector funding** that would support individual projects from our consortium membership of universities, small companies, niche support organizations, and large industry

- Leverages DoD dollars to garner additional outside funds toward developing technologies that **meet dual use requirements** - accommodates a **civilian marketplace** and tries to combine these two communities' needs into viable projects with longer term stability

MTEC
Medical Technology
Enterprise Consortium

What's Different from the Norm?

- MTEC maintains formal cost accounting system for compliance at the enterprise level – performers can use their current system
- MTEC staff actively engages in discussions with potential performers from pre-solicitation announcement until solicitation close date
  - Goal: Better understanding of military need and maturity level desired
  - Result: Better but fewer proposals
- Significant focus on teaming, especially university and industry for commercialization purposes, results in better proposals with less risk of failure
- OTA funding vehicle permits injection of outside dollars
  - Proposals reward outside dollars contribution
  - Venture and industry dollars approached to drive commercialization
  - Joint proposals with other non-profit foundations
- Quicker solicitation-to-award timeline: well within 10 months on average

MTEC
Medical Technology
Enterprise Consortium

Simple Process Flow

- MTEC works with military funding sponsors to identify topics and write solicitations. MTEC also works with members to generate potential topics through white paper submissions.
- Pre-announcements and solicitations sent to membership and outside entities through FBO and website. Only members can propose!!!
- Multiple methods of solicitation to award
- Military and outside funding entities evaluate (not MTEC) to ensure relevance to military needs. Discussions with Offerors often held.
- MTEC issues awards and maintains project oversight until project completes

Process FlowChart

Military → Draft Needs → MTEC →

- Draft Solicitation
- **Pre-Announcement**
- **Technology/Company Outreach**

<u>Solicitation</u>

- RPI
- RPP
  - Direct to Proposal
  - White Paper to proposal
  - **Solution Brief**

Military
MTEC

<u>Pre-Proposal Conference</u>

- Briefing (Tech & Business)
- Q&A
- FAQ Derived & Posted

MTEC R&D Acquisition Methodologies

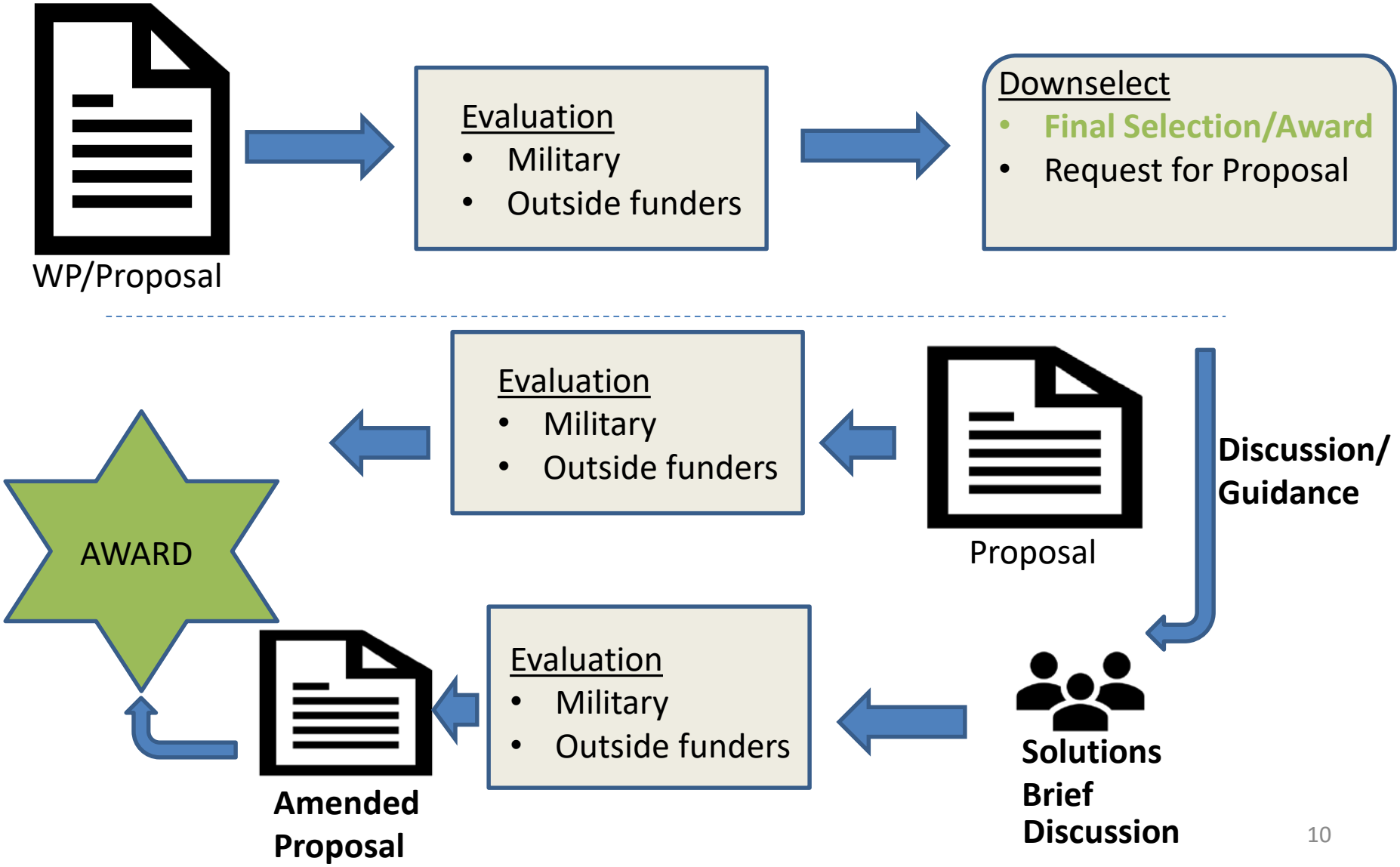
- **Request for Project Information (Market Research)**
  - Information only
  - Used to inform future RPPs

- **Request for Project Proposal (RPP) Methods**
  - Direct to Proposal
    - Small Project Proposal (under $300k) (avg. time to award 4 months)
    - Large Project (avg. time to award 4-6 months)
  - 2 Stage White Paper to Full Proposal (avg. time to award 6-8 months)
  - Commercial Solutions Brief (avg. time to award 8 months)

Tailorable procedures aligned with the complexity, maturity, size (cost), and desired outcomes of the effort

MTEC
Medical Technology Enterprise Consortium

Process FlowChart



MTEC
Medical Technology
Enterprise Consortium

Outside Funders

- Leverage military funding (non-dilutive) with outside dollars to increase the likelihood of R&D success and accelerate the development toward FDA approval and marketing
  - Huge favorable reviews from foundations and outside funders about leveraging non-dilutive dollars
  - Foundations are most willing to collaborate, especially if combined dollars can fund clinical trials
  - Prototype stage makes us more attractive than basic science to venture/industry

- Emphasis on the need for military health protection and restoration from injuries in battle for true philanthropy

MTEC
Medical Technology
Enterprise Consortium

Benefits

Military

- Ability to conduct outreach to scope the proposers
- Ability to discuss and negotiate
- Quicker Timeframe to award
- Potential for Cost Sharing
- Teaming Construction Possible
- Greater Potential for Better Proposals

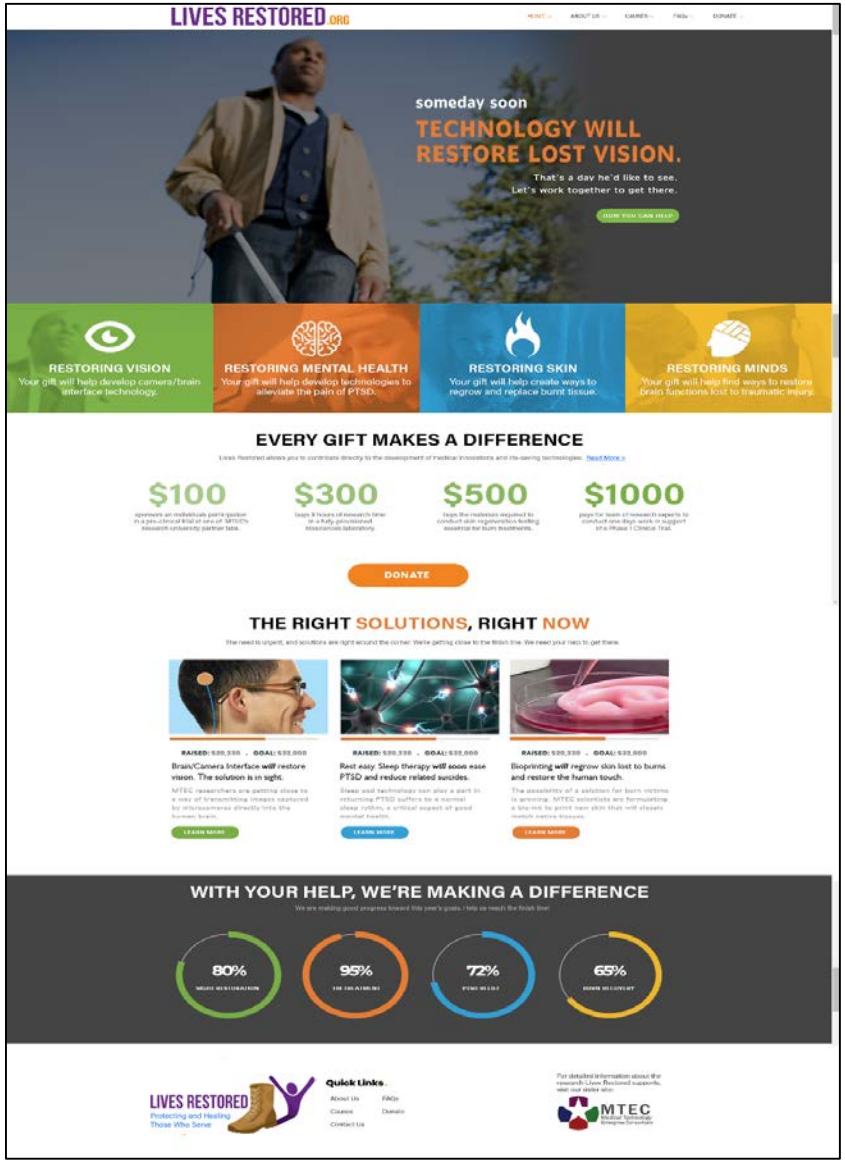
Membership

- Interface with the military at meetings for MTEC & non-MTEC actions
- Pre-Proposal Conference & Discussions during solicitation process
- Greater knowledge of military requirements
- Interface with venture and outside funders
- Better proposals – higher chance of award

MTEC Outreach Efforts for Additional Funding

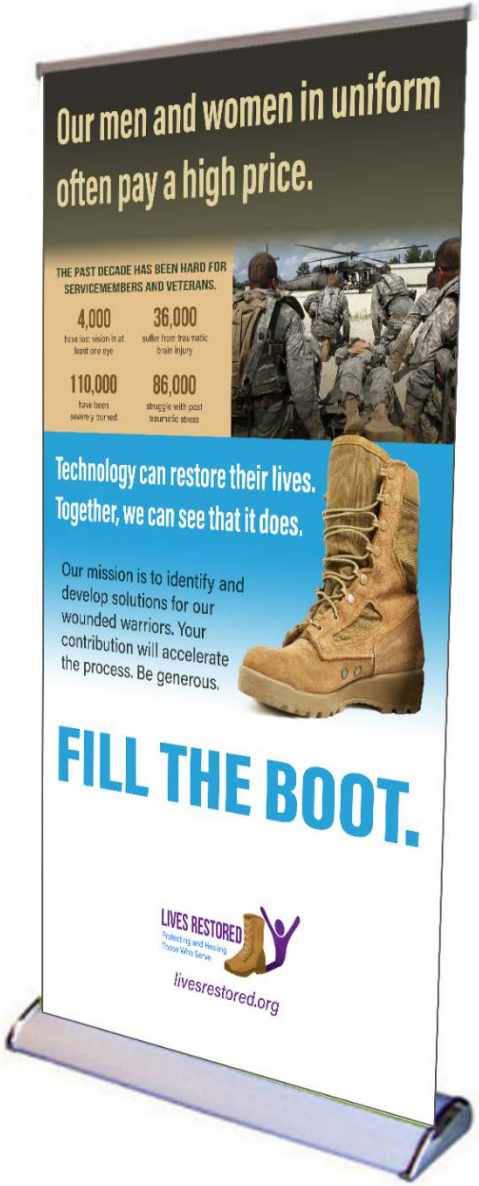
- **Separate Donational Fund Approach – "Lives Restored"**
  - Separate but linked website
  - Corporate Employee donations and matches
  - Events for awareness and fund generation
  - Social Media campaigns

- **Combined Federal Campaign** effort (CFC #24887)



MTEC
Medical Technology
Enterprise Consortium

MTEC Outreach Efforts for Additional Funding



MTEC
Medical Technology
Enterprise Consortium

Points of Contact

- Chief Operating Officer
  William (Bill) Howell
  Tel: 843-345-6864
  Email: William.Howell@tunnellgov.com

- Director of Research
  Dr. Lauren Palestrini
  Tel: 718-619-7570
  Email: Lauren.Palestrini@officer.mtec-sc.org

- Executive Director (Membership)
  Ms. Stacey Lindbergh
  Tel: 843-760-3566
  Email: ExecDirect@mtec-sc.org

Follow us on:

USAISR Burn Center

Overview Brief

Dr. Leopoldo Cancio, MD, FACS
Director
leopoldo.c.cancio.civ@mail.mil
29 March 2019

Overview

Purpose: Informational brief on the United States Army Institute of Surgical Research (USAISR) Clinical Directorate and Burn Center

Outline:

1. Mission & Vision
2. Background
3. Organization Chart
4. Personnel/Multidisciplinary Team
5. Admissions
6. Extracorporeal Membrane Oxygenation (ECMO)
7. Burn Flight Team
8. Readiness Mission
9. Education & Training Mission
10. Burn Flight Team
11. Research Mission
12. Questions

Mission and Vision

» **Mission:**

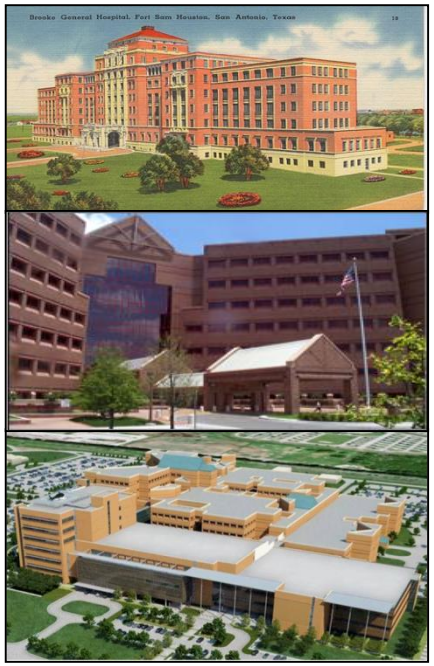
Optimizing Combat Casualty Care

- Optimizing burn wound outcomes
- Prevention, early detection and/or treatment of organ failure
- Rehabilitation, Reconstruction, Resilience (3 ‘R’s of recovery)

» **Vision:**

To be the Nation’s premier joint research organization planning and executing registry-based and translational research providing innovative solutions for burn, trauma, and combat casualty care from the time of injury through rehabilitation.

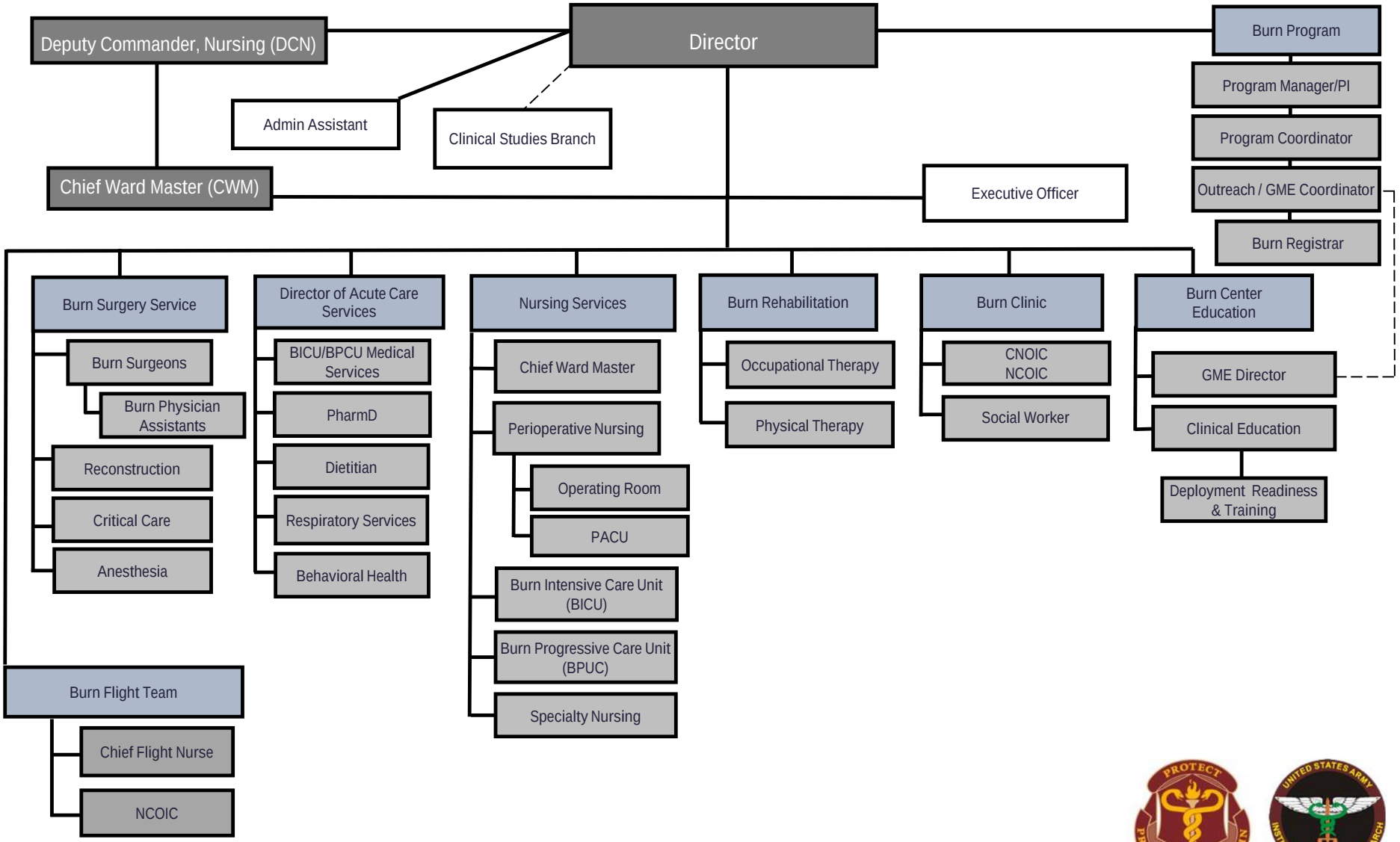
Background



- **USAISR Burn Center active since 1947**
  - Pioneers in burn medicine
  - Old BAMC➔ 1996 New BAMC ➔ 2012 COTO
- **One of 70 verified Burn Centers Internationally**
  - Only Burn Center in DoD
  - 4th largest in U.S. – One of five in Texas
  - Regional Burn Center for 22 counties in South Texas
- **Part of USAISR/MRMC**
  - Research mission
  - Relationship with BAMC
- **Flight Team – Worldwide missions**
- **Comprised of 12 staffed (of 16 total) ICU and 18 staffed (of 24 total) Progressive Care beds**
  - Two Operating Rooms, Outpatient Clinic, Rehab Clinic, Respiratory Therapy Department, ECMO
- **Multidisciplinary Team**

Texas Burn Centers

USAISR Burn Center Organizational Chart



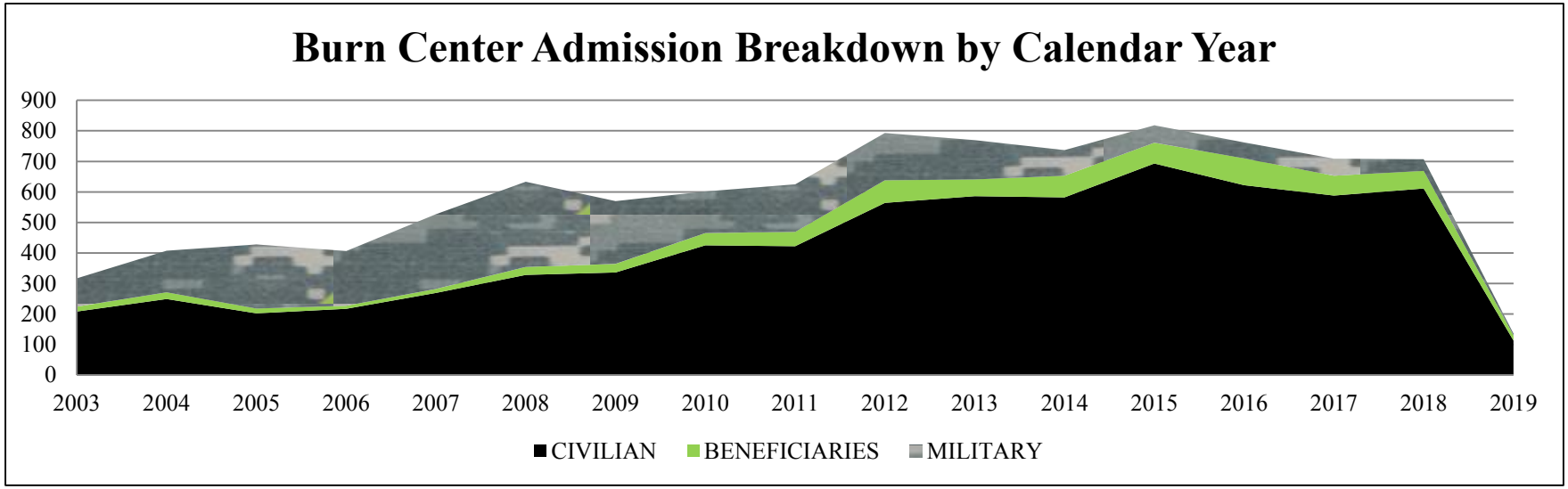
Personnel

Burn Center	MIL	CIV	CTR	TOTAL
Clinical Division	17	11	5	34
Rehab	11	9	13	33
Respiratory	9	3	10	22
Burn Clinic	3	3	4	10
Prog Care (4E)	23	23	19	65
Burn ICU (4T)	29	35	34	98
Peri-Op	12	8	3	23
Education Office	4	1	0	5
	108	**93**	**88**	**289**

Multi-disciplinary Team

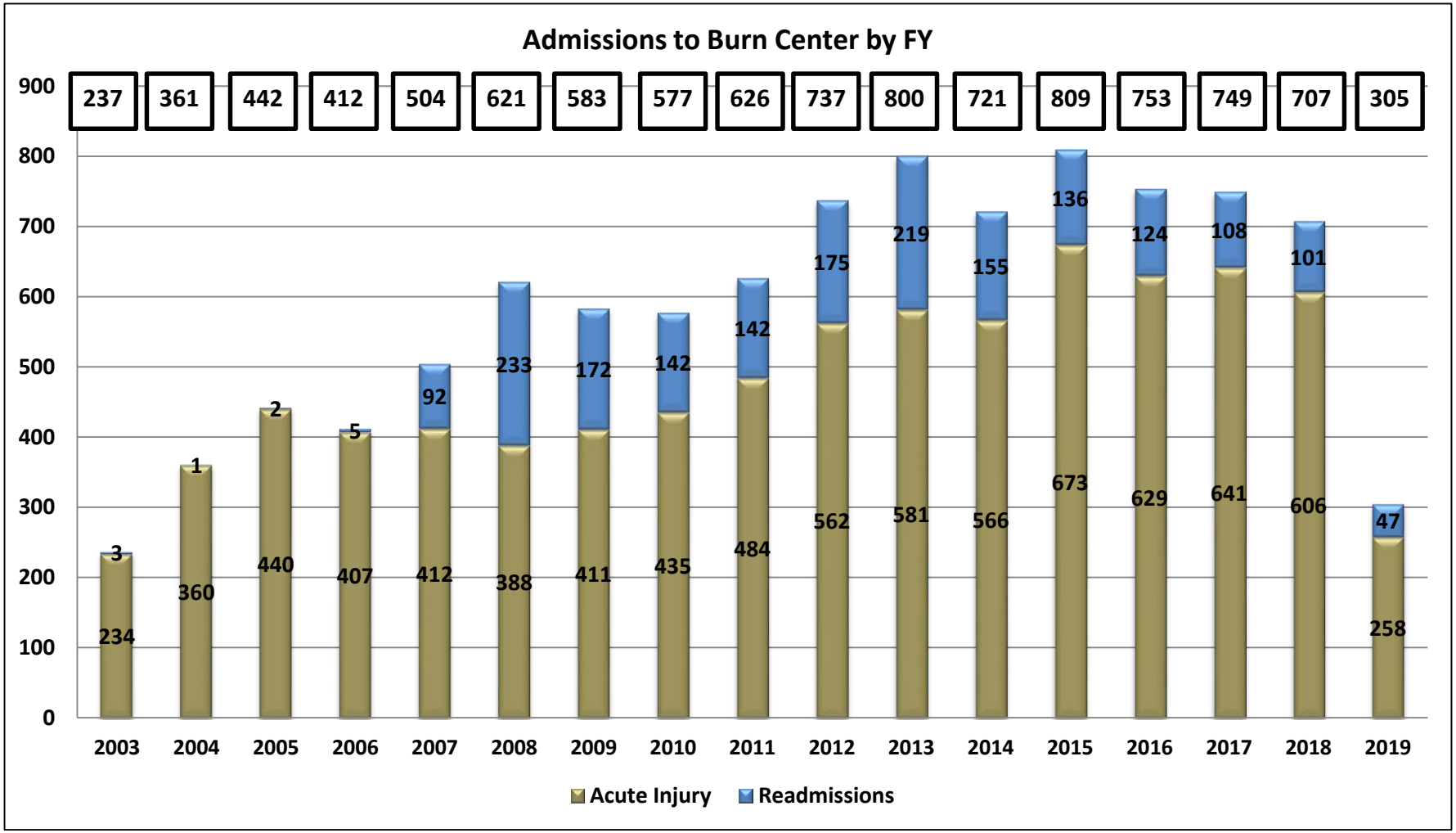
- **Surgeons, Residents, Intensivists, Fellows**
- **Anesthesiologists**
- **Registered nurses, licensed practical nurses**
- **Occupational and physical therapists**
- **Dietitian**
- **Respiratory therapists**
- **Physician assistants**
- **Psychiatric nurse**
- **Social worker**
- **Chaplain**
- **Support services**

Admissions



- » Thermal
- » Electrical
- » Chemical
- » Inhalation Injuries
- » Cold Weather Injuries
- » Combat Casualties
  - Burn Injuries
  - Polytrauma
- » Reconstructive Surgery
- » Toxic Epidermal Necrolysis
- » Stevens-Johnson Syndrome
- » Other Skin Conditions
- » Soft Tissue Skin Infections
- » Non-Burn Wounds

Admit vs. Readmit

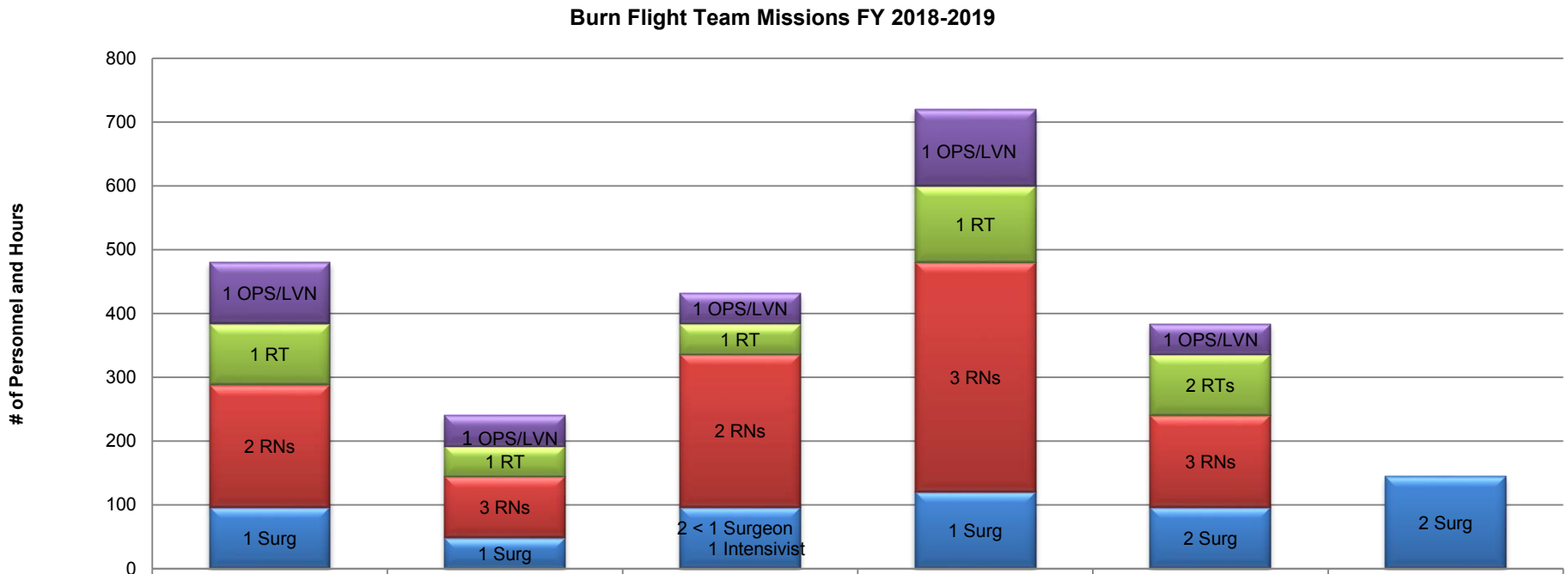


ECMO Mission

- Extracorporeal Membrane Oxygenation (ECMO) therapy
  - » Began in Burn Center
  - » 37 ECMO patients since November 2012
  - » 544 days on ECMO
  - » 76% survivability
  - » 10 transports (6 fixed, 4 ground)

Data as of February 2018

Burn Flight Team Missions FY18-19



	07-10 OCT 2017 San Diego, CA	1-2 DEC 2017 Seattle, WA	7-9 JUN 2018 Guatemala	15-19 JUN 2018 South Korea	3-4 NOV 2018 Landstuhl	14-16 FEB 2019 Birmingham, AL
OPS-LVN hrs	96	48	48	120	48	
RT Hrs	96	48	48	120	96	
RN Hrs	192	96	240	360	144	
Surgeon Hrs	96	48	96	120	96	144
Total Hours away from work center	480	240	432	720	384	144

FY18 – 1,872 hours

FY19 – 528 hours

Education/Training Mission

	FY17 Total	FY18 Total
Burn Flight Team Missions	6	4
Pre-Deployment Burn Training	28	115
GME Resident Burn Rotations	93	63
GME Medical Student Burn Rotations	53	44
GME Intern Burn Rotations	37	27
GME MIL Anesthesia Rotations	8	16
GME Burn Plastic Surgery Rotations	8	5
MIL Army / AF Critical Care Student Burn Rotations	42	29
MIL 68C Student Burn Rotations	78	33
MIL 68V Respiratory Therapist	75	75
MIL 68D Operating Room Tech	35	22
MIL 66E Perioperative Nursing	16	14
MIL 68F Physical Therapy Asst	98	104
MIL 68L Occupational Therapy Asst	11	10
Total Trained	**582**	**557**

Clinical Research

- Chief – LTC Kevin Akers, MD
- 16 personnel in CRSB (+3 contract RN vacancies)
- Budget ~$2M
- 32 active protocols
  - 17 prospective (4 FDA)
    - 2 in development (1 FDA)
  - 15 retrospective
- 33 peer reviewed publications in FY16
- Collaboration of clinical and bench scientists

Questions

Burn and Soft Tissue Research

Robert J. Christy, PhD, Chief, Burn Injury Research
MAJ Stephen Crimmins, Chief, Battlefield Pain Research

Scope of Military and Civilian Burn Injuries

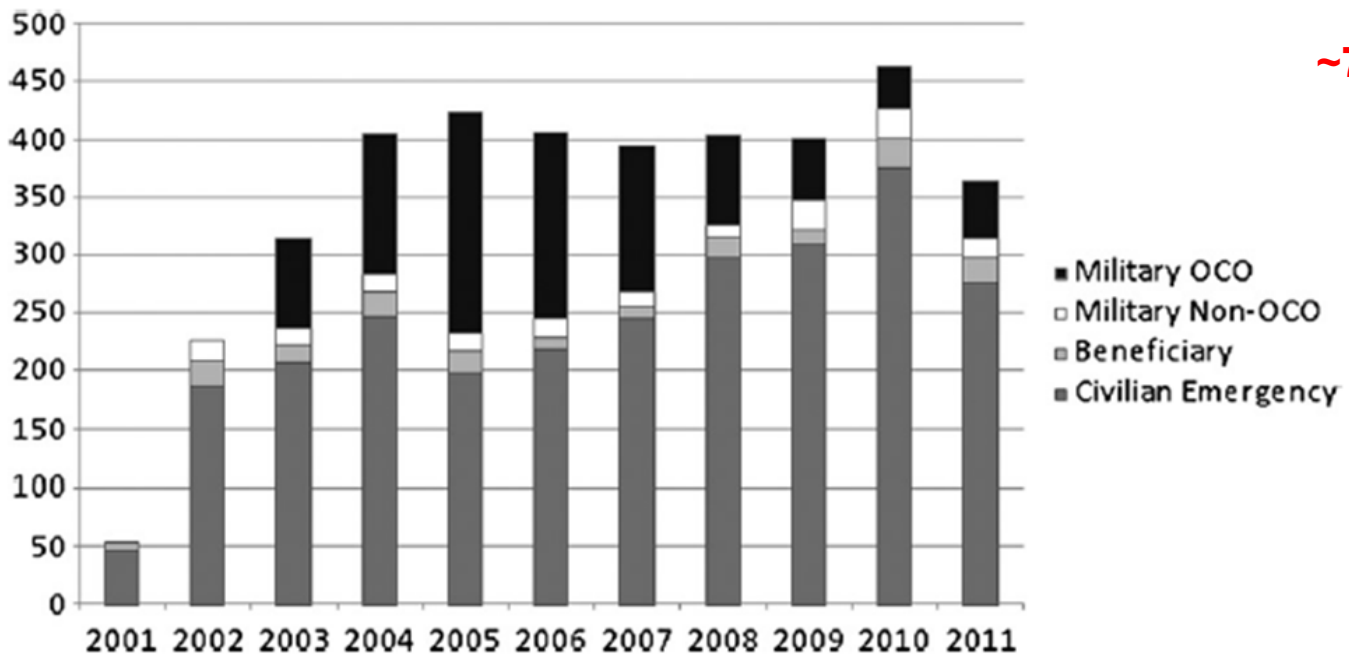
Every year in the United States more than

- ~500k people received medical treatment for burn injuries
- 40,000 required hospitalization

Associated costs

- Burns: $10 billion
- Skin scarring: $12 billion

USAISR– Burn Center Admissions



Last few years have averaged ~700 patients total

Burn Injuries Account for **5-10%** of Combat Casualties

J Trauma Acute Care Surg., 2012,73 (S5), S409-4016 ; Burn Incidence and Treatment in the United States: 2016
http://www.ameriburn.org/resources_factsheet.php.

Combat Burn Injuries

Burn Injuries Account for 8-11% of Combat Casualties (CCs)

Small Burns (<20% TBSA) are 80% of the CCs

Treated Role I-III and remain in theater w/o evacuation

Accomplished by having:
1) Field deployable device to assess burns
2) Deployable therapies for burns
   a) Conversion Inhibitors
   b) Infection Prevention and Management
   c) Non-Surgical Debridement
   d) Temporary Coverage
   e) Resuscitation

In theater RTD

Large Burns (>20% TBSA) are 20% of the CCs

Evacuated to Role IV (USAISR)

Accomplished by having:
1) Improved skin substitutes
2) Temporary coverings
3) Autograft sparring

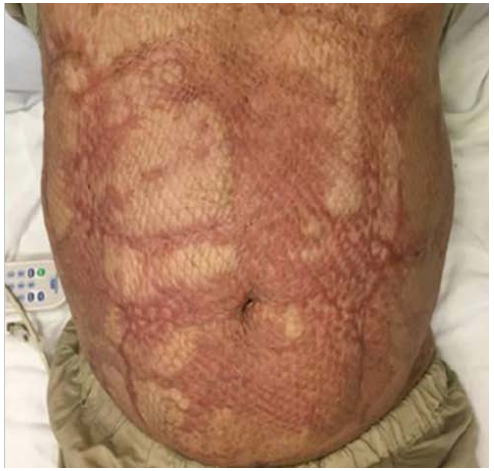
Delayed RTD

J Trauma Acute Care Surg., 2012,73 (S5), S409-4016 ; Burn Incidence and Treatment in the United States: 2016
http://www.ameriburn.org/resources_factsheet.php.

Burn Injury Research

With current focus on Prolonged Field Care (PFC) and anticipation of conflicts with near-peer adversaries, focus has shifted to solutions that can be employed farther forward in the continuum of care.

- Burn conversion prevention
- Temporization of wounds and infection prevention
- Non-surgical debridement



Identify materiel solutions to improve survival and recovery after combat-related burn injury that will result in decreased hospitalization time, quicker return to duty, and improved cosmetic and functional outcomes.

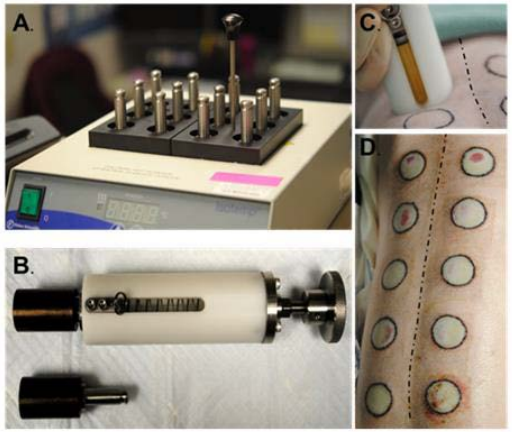
Preclinical Porcine Burn Models

1 cm Excision

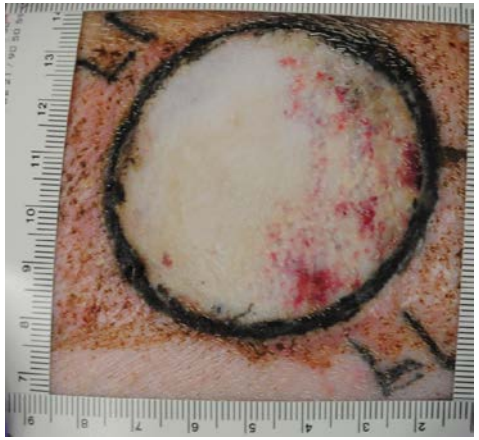
Non-infected

Infected

3 cm Partial/ Full Thickness Burn



6 cm Partial/ Full Thickness Burn

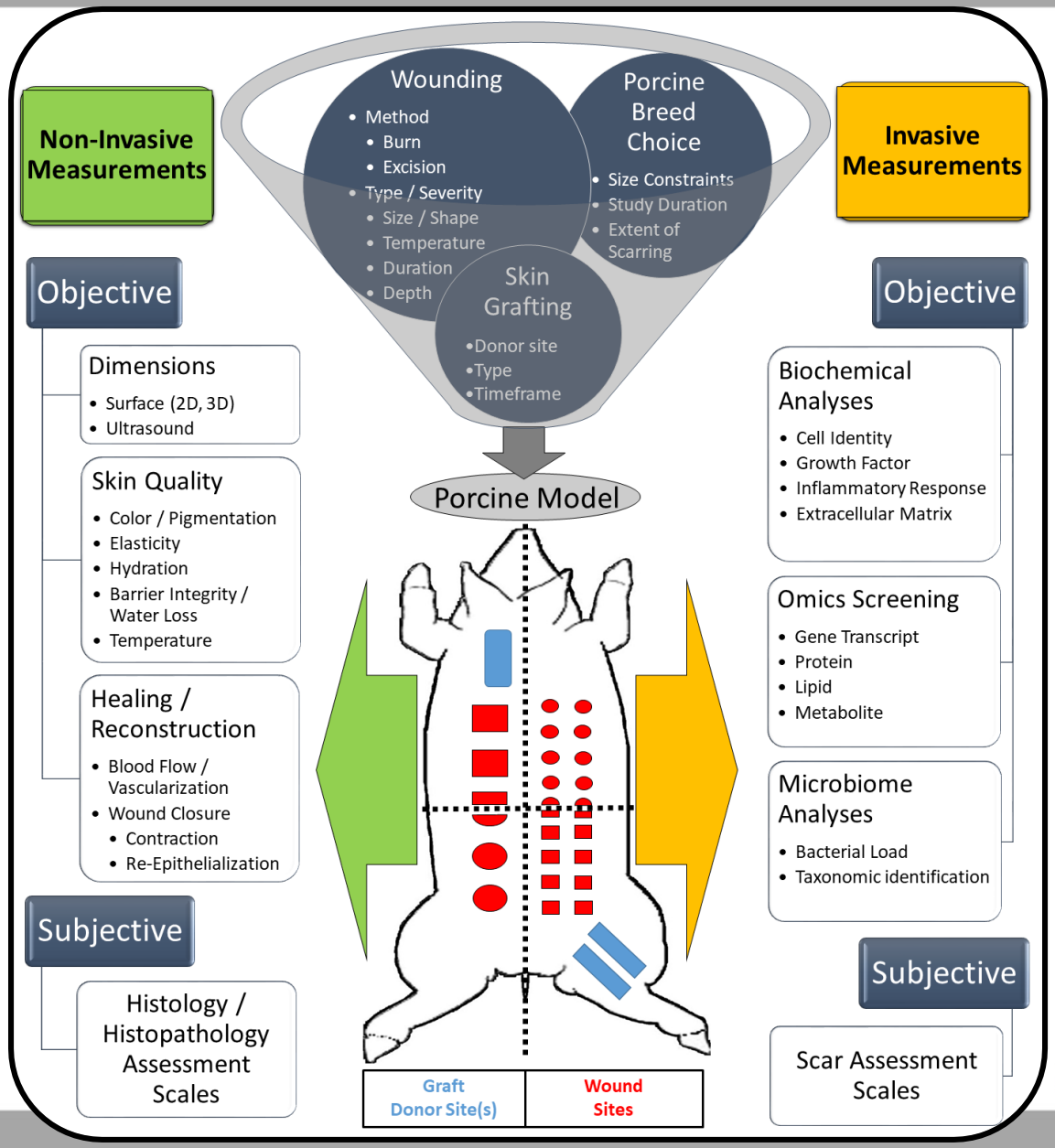


Thermocoupled Brass Blocks

Square:5 and 7.5 cm
Circle: 3 and 6 cm
Rectangle: 9x15 cm

Large TBSA Burn (9x15 cm)

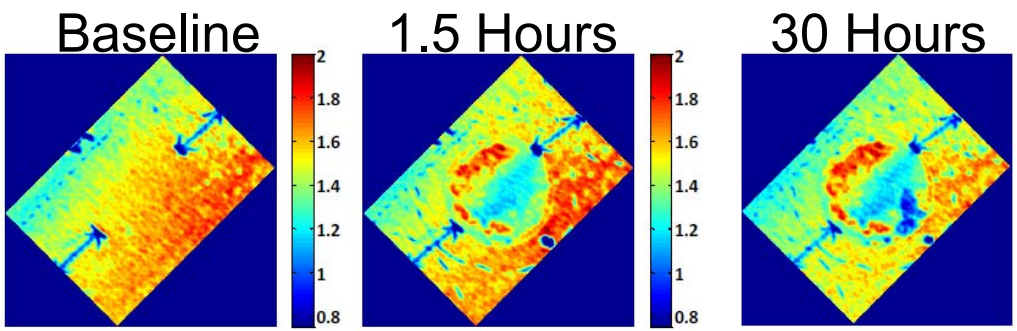
Outcome Measurements



Non-Invasive Imaging Devices to Assess Burns

Spatial Frequency Domain Imaging

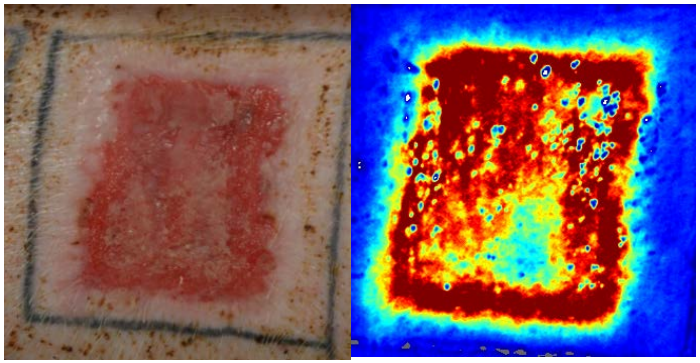
Beckman Laser Institute



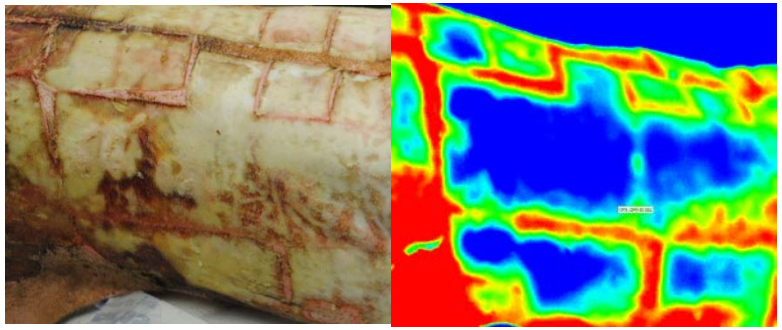
Laser Speckle

Moor Inc. (commercial device)

Beckman Laser Institute

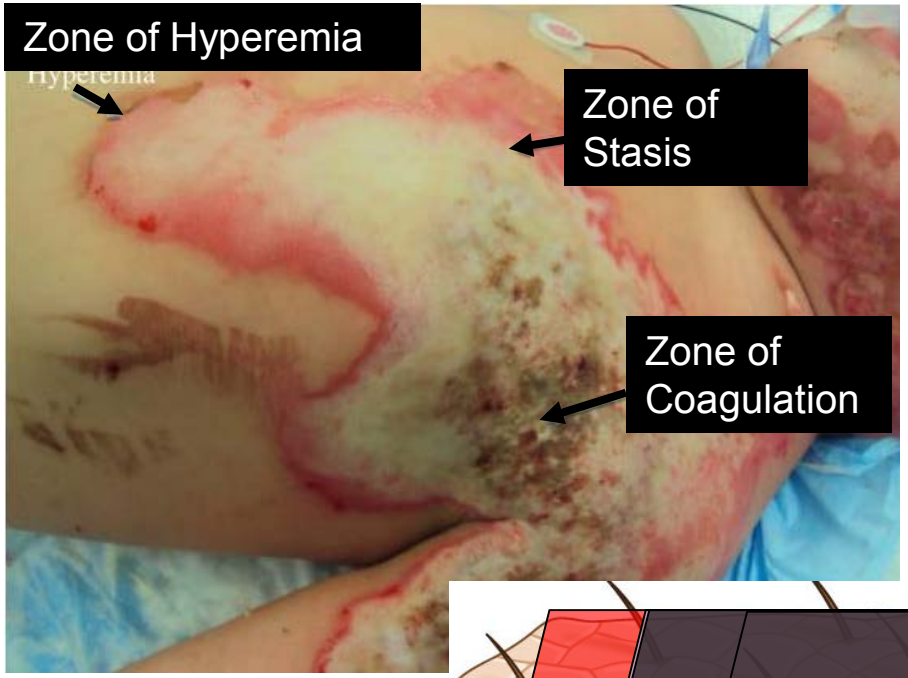


Silhouette Imaging



FLIR

Burn Conversion



Zone of Coagulation - irreversible tissue loss due to coagulation of the constituent proteins.

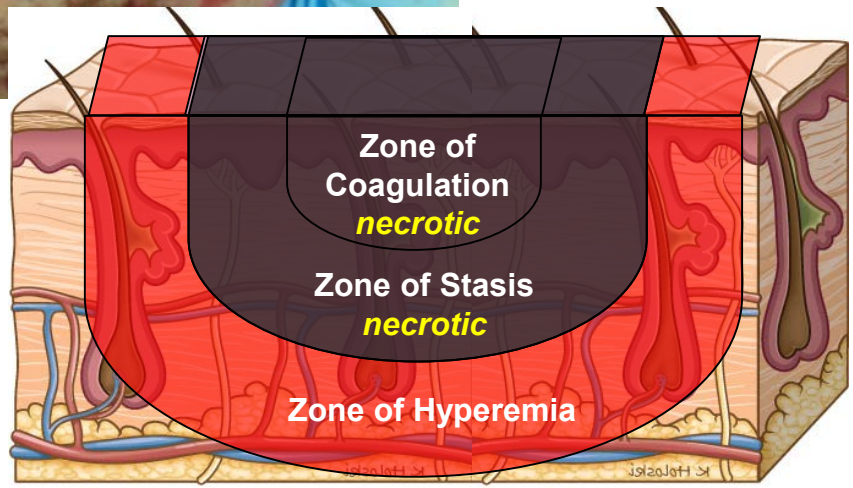
Zone of Stasis - decreased tissue perfusion. The tissue in this zone is **potentially salvageable**.

Zone of Hyperemia - tissue perfusion is increased; the tissue here will recover.

Lateral + Vertical Progression

↓

Full-Thickness Injury



Superficial

Superficial Partial-Thickness

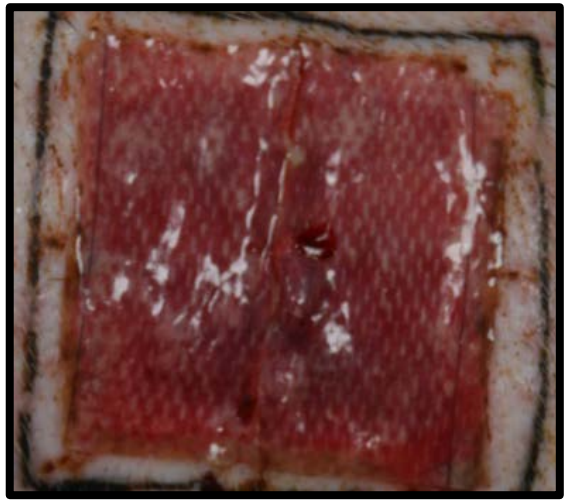
Deep Partial-Thickness

Full-Thickness

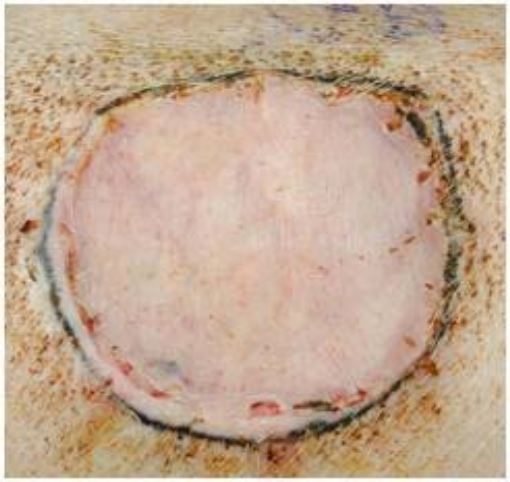
Prevent/Mitigate Infection

Infected

Graft Failure



Non-Infected

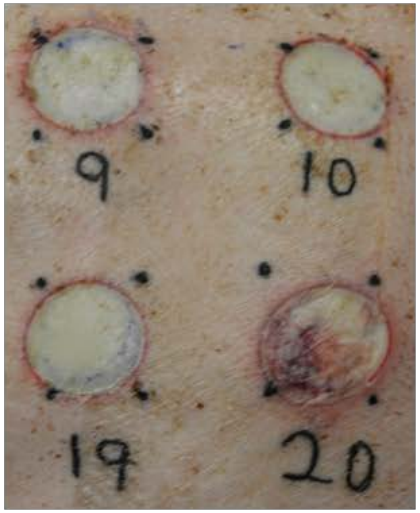


Graft Success

Non-Surgical Debridement

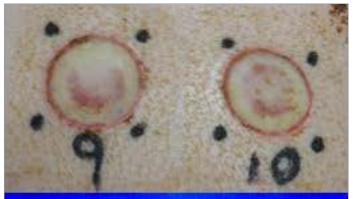
Create Burns

100 C°



Apply Non-Surgical Enzymatic Debridement Agents

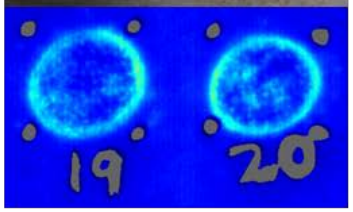
Assessment of Debridement and Wound Healing



No Debridement

No Debridement = No Perfusion

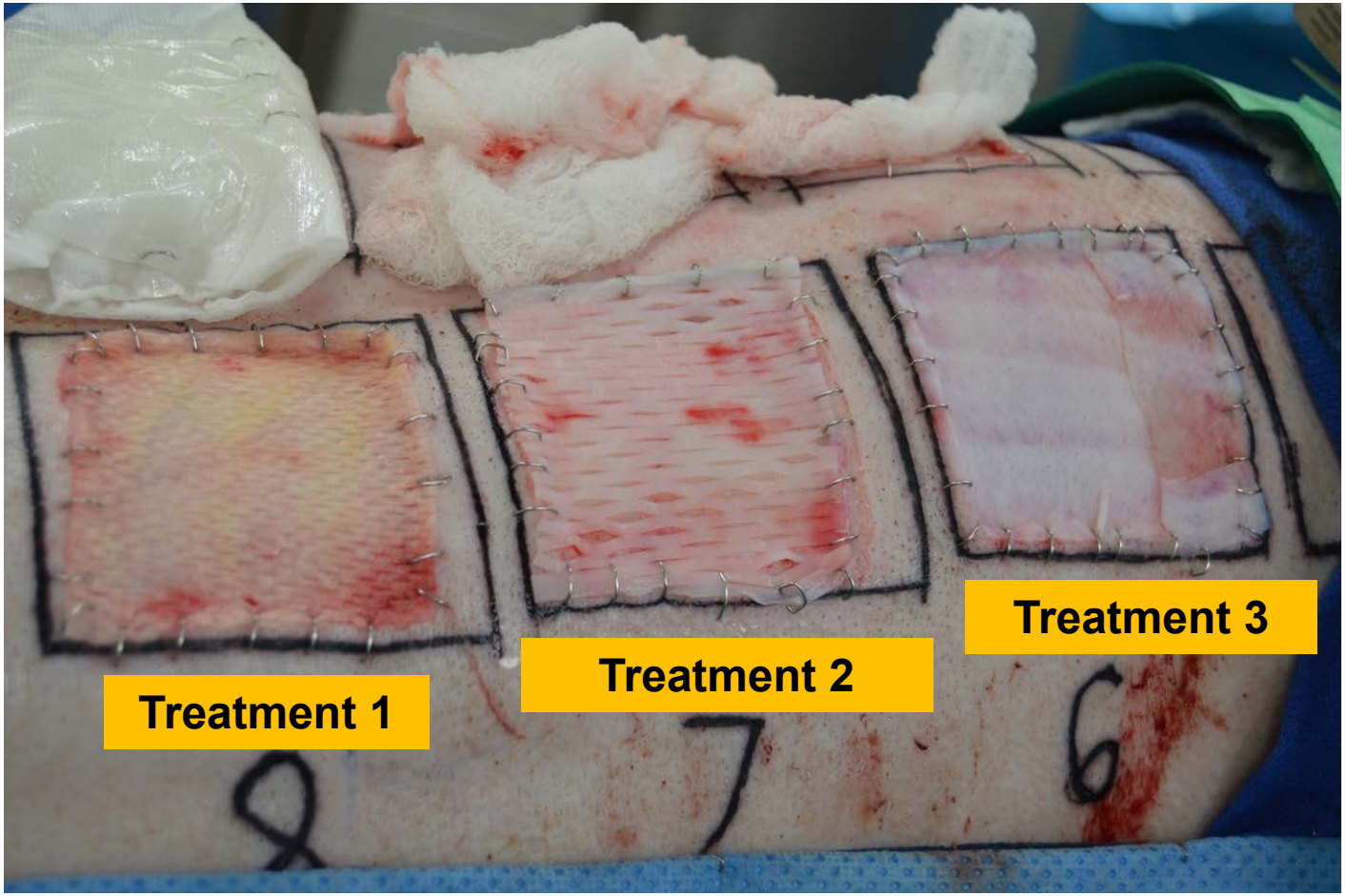
Adequate Debridement



Adequate Debridement = Perfused Wound Bed

Non-surgical debridement options could be applied to burn wounds in theater to reduce healing times.

Temporary Skin Coverings

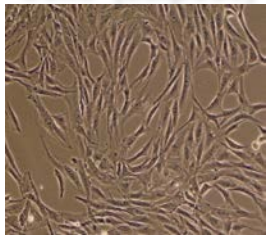


After a wound is adequately debrided, what is the best option to temporarily cover the wound.

Past Accomplishments

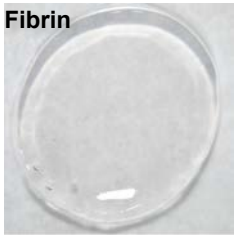
Products

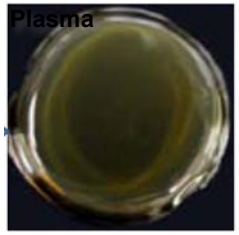
Human Stem Cells (adipose)



Amniotic Membrane (AM)

Hydrogels





Extracellular Matrices

Accomplishments

Amniotic Membrane:
- Preparation process optimized
- Preclinical evaluation completed

Stem cells:
- Isolation and optimization completed
- Preclinical evaluation completed

Fibrin Hydrogels:
- Preparation process optimized.
- Preclinical evaluation completed.
- Patented technology

Plasma-based Hydrogels :
- Preparation process optimized
- Preclinical evaluation completed
- Clinical Evaluation planned

Extracellular matrices (ECM):
- Preparation process for dermal hypodermal and muscle ECM optimized
- Preclinical evaluation completed
- Clinical Evaluation planned

Transition Products

Amniotic Membrane:
- Freeze-dried
- Antimicrobial delivery

Stem cells-derived products
- Stem cell derived exosomes
- Adipose derived stem cells
- Lipogems

Plasma Hydrogels:
- Freeze-dried plasma based dressing
- Antimicrobial dressing
- Wound dressing for pain management

Extracellular matrices (ECM):
- ECM for immediate burn care/soft tissue coverage
- Tissue sparring wound dressings
- Regenerative soft tissue replacement matrices

Battlefield Pain

MAJ Stephen Crimmins

Battlefield Pain

- Pain will impact every person, including military personnel, and can manifest in a variety of ways and with a variety of intensities
  - Pain on the battlefield will inhibit the ability of Soldiers and combat units from completing mission requirements
- Current treatments for pain heavily depend on opioid based drugs the side effects of which include:
  - Physiological changes like respiration rate
  - Cognitive decline
  - Tolerance and addiction
- Pain thresholds and sensitivity can be changed by psychological modifiers including stress
- Pain assessment and resolution currently requires qualitative self-reporting from a patient
  - Pain assessment is greatly hindered in non-communicative patients including those with facial trauma

Battlefield Pain

- How can pain be managed on the battlefield in such a way that:
  - Allows an injured Soldier to still participate in the mission
  - Prevents the formation of chronic pain during extended operations
- How can pain be measured far forward so that:
  - Pain levels are objective
  - Pain generation and resolution can be monitored
  - Pain medication is precisely dosed to preserve limited supplies
- How can different approaches be used to change pain threshold levels:
  - Antidepressants and anxiolytics
  - Resiliency training

Battlefield Pain

- Mission – Study acute pain from point of injury on the battlefield through the entire continuum of treatment with focus on prolonged field, role 1, and role 2 medical care in order to maintain Soldier lethality and prevent the degradation of collective unit function.

- The goals of the Task area are:
  - Reduce opioid use
  - Mitigate physiological side effects of analgesics
  - Mitigate psychosocial effects on pain
  - Identify pain biomarkers

- Scientific Thrust Areas
  - Preclinical testing of novel non-opioid drugs
  - Physiological effects of analgesics
  - Psychosocial effects on pain
  - Pain biomarker discovery

Battlefield Pain Management

Development Pipeline – Current Snapshot of Functional R&D Stages

Discovery-Knowledge (6.1/6.2/6.3)
Topic Areas
TRL 1-3

- Identify and Characterize Molecular Changes and Biomarkers of Pain
- Characterize the pathophysiology of pain mechanisms
- Characterize the impact of stress on analgesic efficacy and perception of pain
- Development and characterization of relevant animal models of pain

Discovery-Product (6.2/6.3)
Specific Candidate Concepts/Drugs/Devices
TRL 3-4

- Pre clinical evaluation of non-opioid analgesics
- Physiological impact of analgesics in polytrauma and shock (with TCCC)
- Combination therapies for analgesics – polypharmacy, analgesic synergy
- Develop and verify pain biomarker panel

Late Discovery/Transition (6.3)
Pre-clinical & Early Clinical Studies
on Selected Lead Concept/Drug/Device Expected Transition w/in 2 yrs
TRL 4-5

- Clinical trials with novel analgesics
- Clinical trials with pain biomarker panel

- No 6.3 core funding for Battlefield Pain

Full (Clinical) Development (6.4/6.5)
Specific Product
TRL 5-9

- TBD

Knowledge Products To Support Clinical Practice.
- TBD (pending steering committee input)

Go/no go decision gate

Current Projects

- Volatile Non-Opioid Analgesics
- Evaluation of Intrathecal Ketamine
- Therapeutic Potential of Exosomes
- Novel Acetaminophen Analogs
- Integrated –Omics Study of Pain
- Unpredictable Stress and Pain Sensitivity
- Exosome Mediated miRNA Transfer in Pain

Assessing the efficacy of novel compounds on acute pain

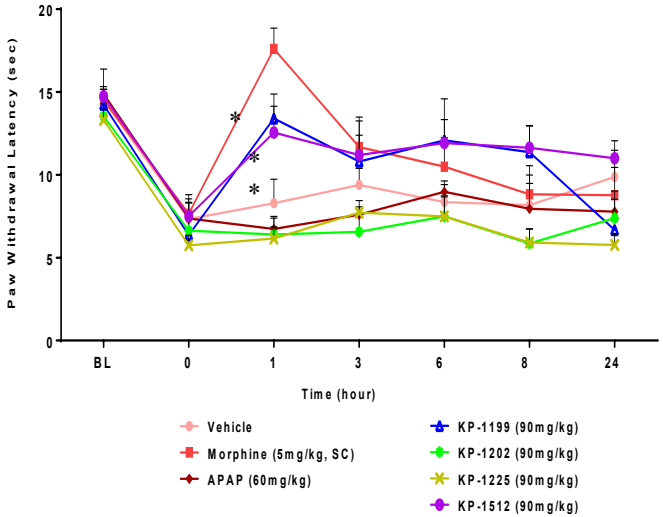
Study/Product Aim(s)

- Aim 1: analyze behavioral effects of novel analgesics in rat models of pain
- Aim 2: determine effects of novel analgesics on opioid efficacy and dosage requirements
- Aim 3: develop a rat model of visceral pain
- Aim 4: develop a pig model of thermal injury pain

Approach

Novel compounds with analgesic potential will be tested in a rat model of full thickness thermal injury. Mechanical allodynia and thermal hyperalgesia will be used to determine the behavioral responses to pain. Dose and time response curves for all compounds will be determined. The effect of the compounds on opioid dosage requirements (analgesic synergy) will be determined by isobolographic analysis. A rat model of visceral pain will be created through partial constriction of the superior mesenteric artery. A pig model of thermal injury will be created using the partial thickness thermal injury model currently used in the department.

Effects of Morphine, APAP, and APAP Analogs on Thermal Hyperalgesia in a Rat Model of Thermal Injury



Timeline and Cost

Activities	FY 19	FY 20	FY 21
Aim 1: analyze behavioral effects of novel analgesics in rat models of pain			
Aim 2: determine effects of novel analgesics on opioid efficacy and dosage requirements			
Aim 3: develop a rat model of visceral pain			
Aim 4: develop a pig model of thermal injury pain			
Estimated Budget ($K)	**$2,109**	**$2,001**	**$2,163**

Goals/Milestones

FY19 Goal – Complete analysis for 1st novel compound

- ☐ Analysis of dose and time response curve for 1st novel compound
- ☐ Analysis of opioid analgesic synergy for 1st novel compound
- ☐ Analysis of dose and time response curve for 2nd novel compound

FY20 Goals – Complete analysis for 2nd and 3rd novel compound

- ☐ Analysis of opioid analgesic synergy for 2nd novel compound
- ☐ Analysis of dose and time response curve for 3rd novel compound
- ☐ Analysis of opioid analgesic synergy for 3rd novel compound
- ☐ Analysis of dose and time response curve for 4th novel compound
- ☐ Completion of rat model of visceral pain

FY21 Goal – Complete analysis for 4th novel compound

- ☐ Analysis of opioid analgesic synergy for 4th novel compound
- ☐ Perform pilot experiments for any additional compounds from developers
- ☐ Write and submit manuscripts
- ☐ Write follow-on proposal using pilot data
- ☐ Completion of pig model of thermal injury pain

Updated: 4 FEB 2019

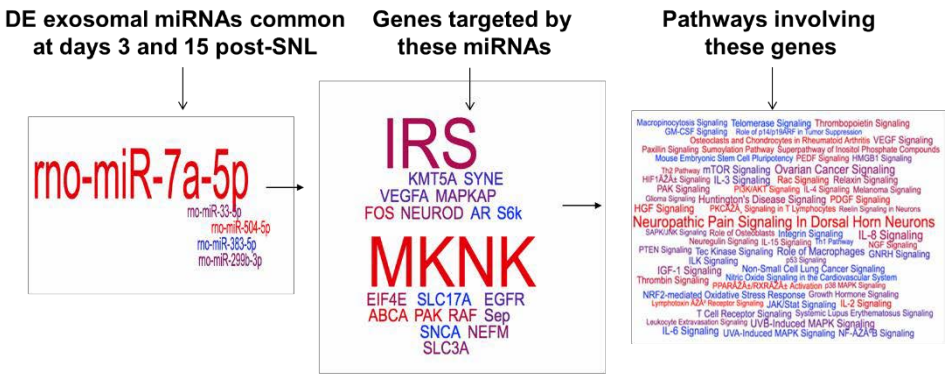
Investigate exosomal miRNA as potential biomarkers, therapeutic targets, and treatments for trauma-induced pain at the point of injury through Role 2 level of care

Study Aim(s)

- Investigate injuries that induce acute pain for blood plasma exosome composition *in vivo*
- Elucidate the functional and therapeutic role of exosomes and their miRNA cargo

Approach

Isolate exosomes and tissue from *in vivo* injury induced pain models and perform biomarker assays (multi-omics). Treat injured rats with exosomes derived from naïve rats or target differentially expressed (DE) exosomal miRNAs at the point of injury and monitor pain development.



Genes and pathways regulated by DE exosomal miRNAs at both day 3 and 15 post-SNL
The 33 exosomal miRNAs DE at both day 3 and 15 were filtered down to 5 microRNAs that down regulate 19 experimentally validated targets. These targets are involved in a number of pathways important in the development of neuropathic pain. These include neuropathic pain signaling in the dorsal horn neurons, inflammatory pain pathways such as IL signaling, and the VEGF, mTOR and MAPK signaling pathways. Size indicates the number of times that gene/ miRNA appeared in the list. The genes/pathways regulated by a specific miRNA are all the same color.

Timeline and Cost

Activities / CY	19	20	21	22
Behavioral pain assays, sample isolation and prep				
Multi-omics and data analysis				
Exosome and miRNA mimic exp				
Manuscript submissions				
Estimated Budget ($K)	**$748**	**$752**	**$752**	

Goals/Milestones CY18

Goal

Animal Protocol Submission and IACUC/ACURO Approval

CY19 Goals

- ☐ Begin exosome and their miRNA cargo affect on pain
- ☐ Exosome and tissue collection

CY20 Goal

- ☐ Multi-omic data analysis

CY21 Goal

- ☐ Complete exosome and their miRNA cargo affect on pain
- ☐ Complete multi-omic data analysis
- ☐ Manuscript submissions

Comorbid symptoms of acute burn pain and depression

Hypothesis: We hypothesize that thermal injury alters the brain-derived neurotropic factor (BDNF) system contributing to comorbid symptoms of pain and depression.

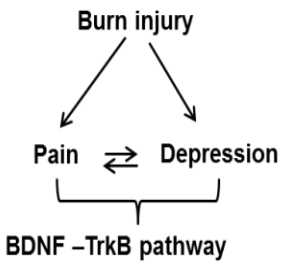
Specific Research Aims:

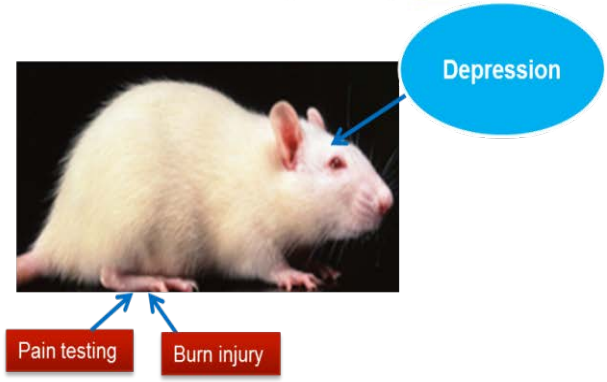
Specific Aim 1 will characterize an animal model of comorbid symptoms of burn pain and depression.

Specific Aim 2 will investigate burn induced pain and depression mediated changes in BDNF expression.

Specific Aim 3 will examine the effects of the antidepressant tianeptine on burn induced symptoms of pain and depression.

Approach/Methods: An animal model of comorbid symptoms of burn pain and depression will be developed by inflicting rats with thermal injury and then characterizing the development of pain and depressive-like behaviors over a period of time. The involvement of the BDNF system in a co-existing state of post-burn pain and depression will be examined using a biochemical, pharmacological, and molecular biology approach. Additionally, the effects of standard antidepressant and analgesics will be studied using a behavioral approach.





Milestones and Deliverables:

FY18 Goals – Develop an animal model of comorbid symptoms of burn pain and depression

☐ Write an animal protocol and obtain IACUAC approval to perform animal experiments

☐ Complete animal behavioral experiments

☐ Bank tissues for molecular and histological analysis

☐ Analyze the data

FY19 Goals – Investigate burn induced pain and depression mediated changes in BDNF expression

☐ Complete time-dependent animal behavioral experiments

☐ Bank tissues for in vitro assays

☐ Complete the analysis of tissues for BDNF and TrkB expression using RT-PCR, ELISA, and Western blot techniques

FY20 Goals – Examine the effects of the antidepressant tianepatine in attenuating pain and depression

☐ Complete behavioral experiments to determine if tianeptine alleviates symptoms of pain and depression induced by burn injury

☐ Analyze data, present at in meetings, write and publish manuscripts

Timeline and Cost

FY	19	20	21
Aim 1. Development of an animal model of comorbid symptoms of burn pain and depression.			
Aim 2. Involvement of burn induced pain and depression on BDNF expression.			
Aim 3. Effects of tianeptine on comorbid symptoms of burn pain and depression.			
Proposal Budget ($K)	401K	433K	417K

QUESTIONS???

Orthopaedic Trauma

Burden of Injury, Current Efforts, and Future Opportunities

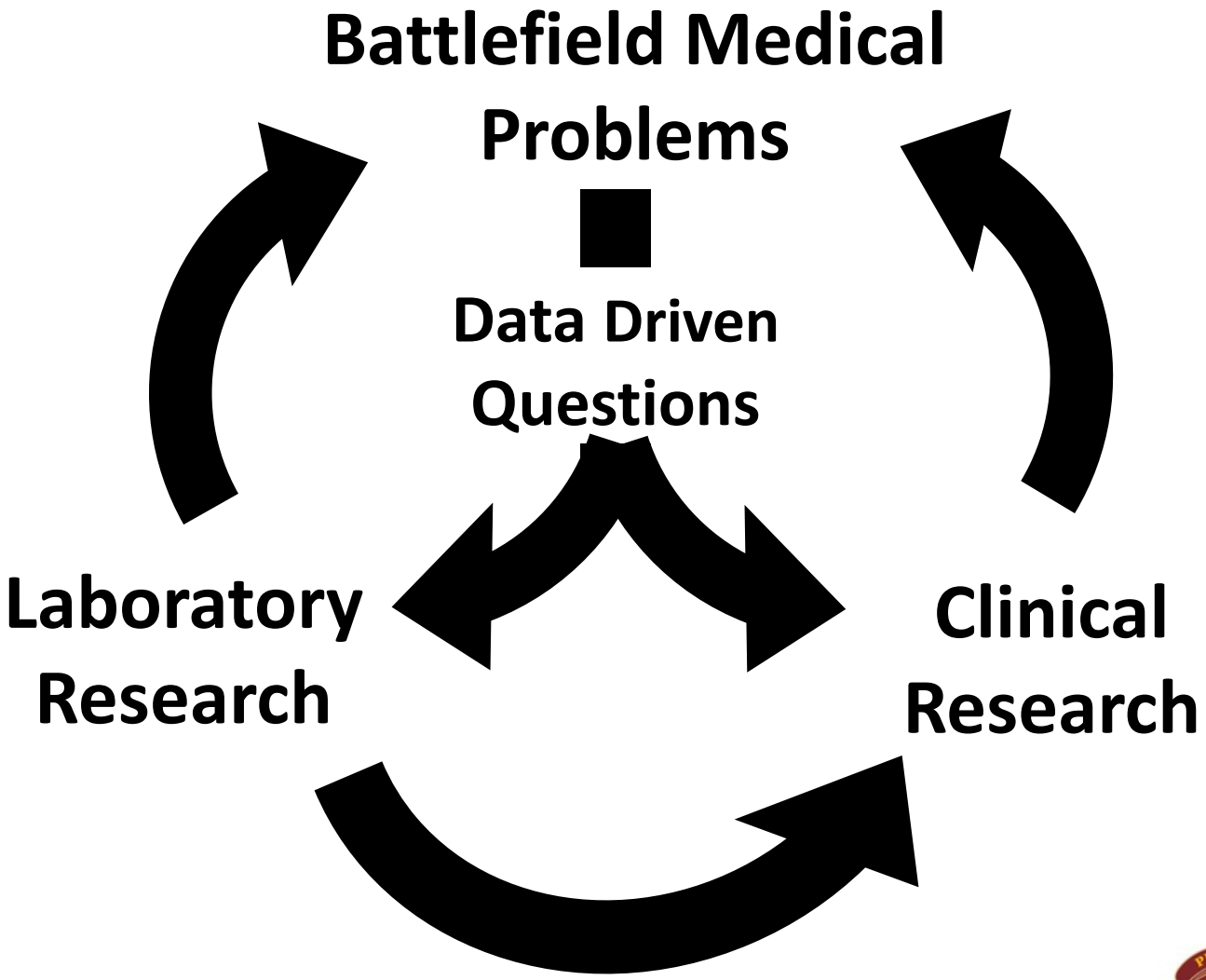
Joseph C. Wenke, PhD

28 March 2019

Disclaimer

The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

The Research Philosophy of The U.S. Army Institute of Surgical Research



Comparison of Statistics for Battle Casualties, 1941-2013

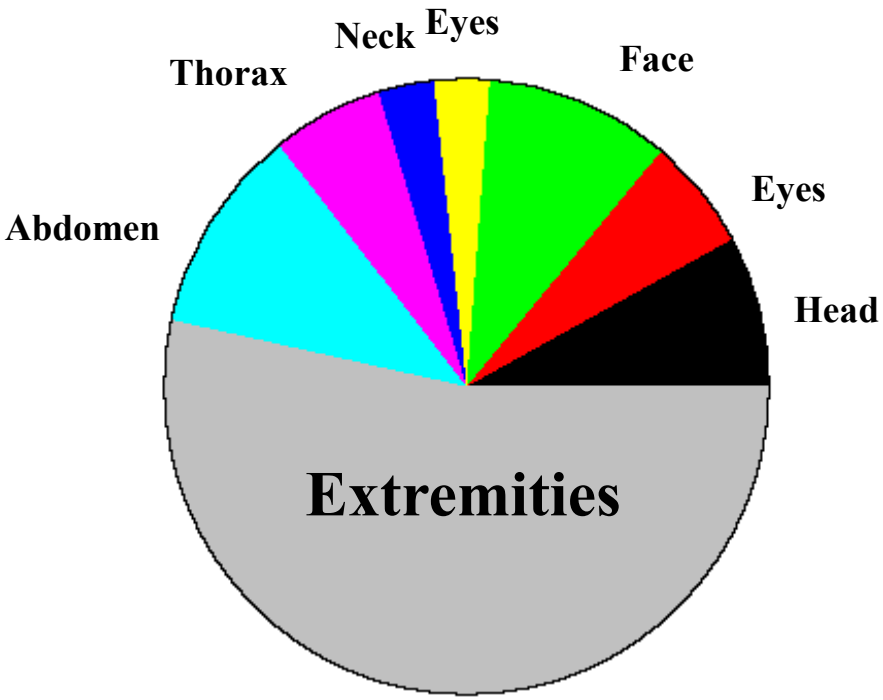
	World War II	Vietnam War	Iraq & Afghanistan
Overall mortality of those wounded in combat	22.8%	16.5%	8.8%

Characterization of Extremity Wounds in Operation Iraqi Freedom and Operation Enduring Freedom

Brett D. Owens, MD, John F. Kragh, Jr, MD, Joseph Macaitis, BS, Steven J. Svoboda, MD, and Joseph C. Wenke, PhD

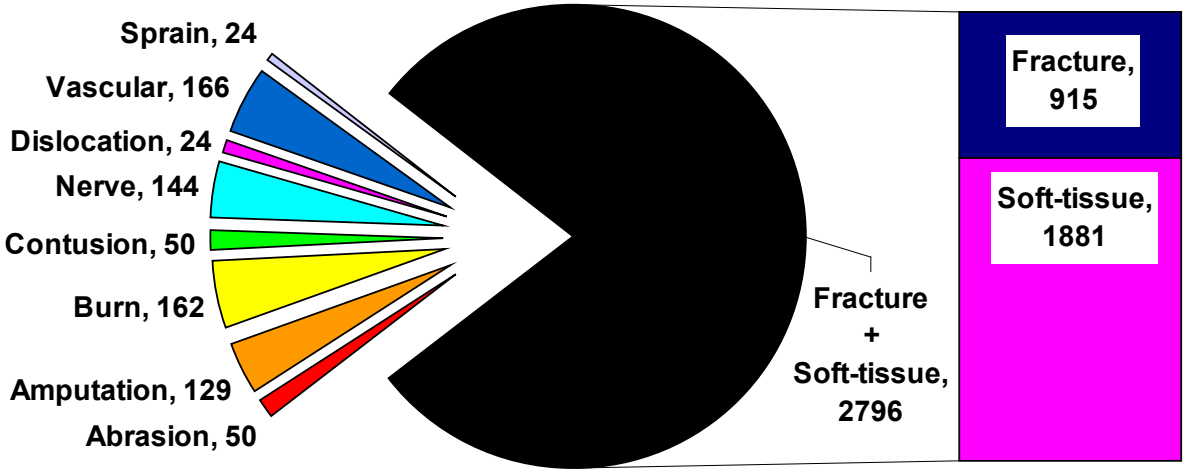
(*J Orthop Trauma* 2007;21:254–257)

- » 1,566 soldiers sustained 6,609 combat wounds
- » 3,575 were extremity wounds (**<u>82% of the soldiers had at least one extremity wound</u>**)
  - » For every injured soldier there are 2.3 extremity wounds



Extremity Injuries

- 53% of the extremity injuries were penetrating soft tissue wounds (1.2 for every injured Soldier)
- 26% were fractures (1 open fracture for every 2 injured Soldiers)

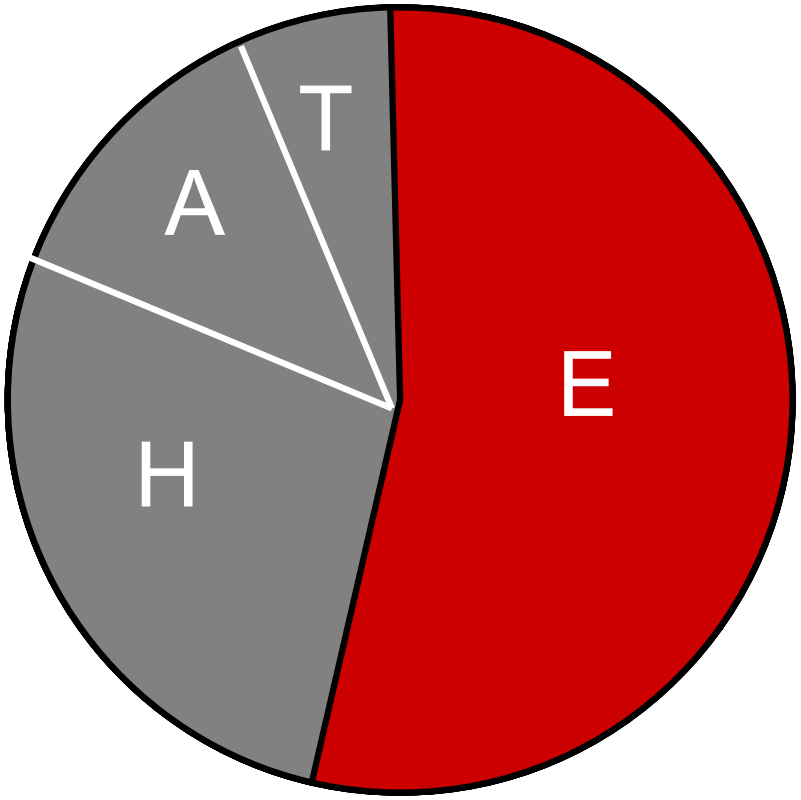


Injuries

Resource Utilization and Disability Outcome Assessment of Combat Casualties From Operation Iraqi Freedom and Operation Enduring Freedom

Brendan D. Masini, MD, Scott M. Waterman, MD,* Joseph C. Wenke, PhD,* Brett D. Owens, MD,† Joseph R. Hsu, MD,‡ and James R. Ficke, MD‡*

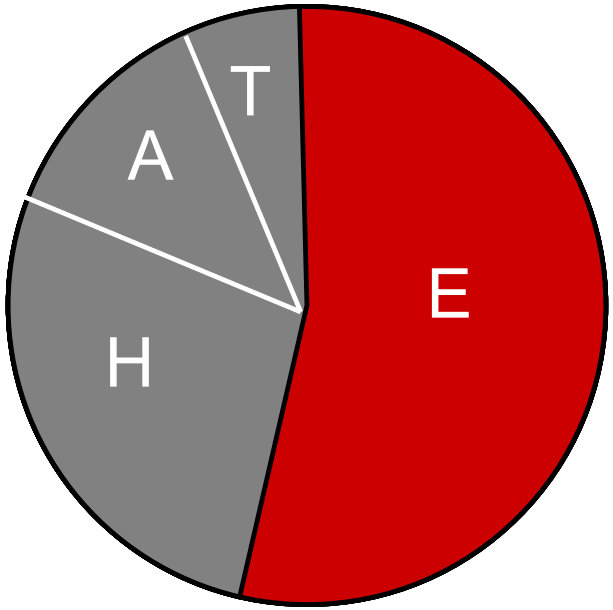
J Orthop Trauma • Volume 23, Number 4, April 2009



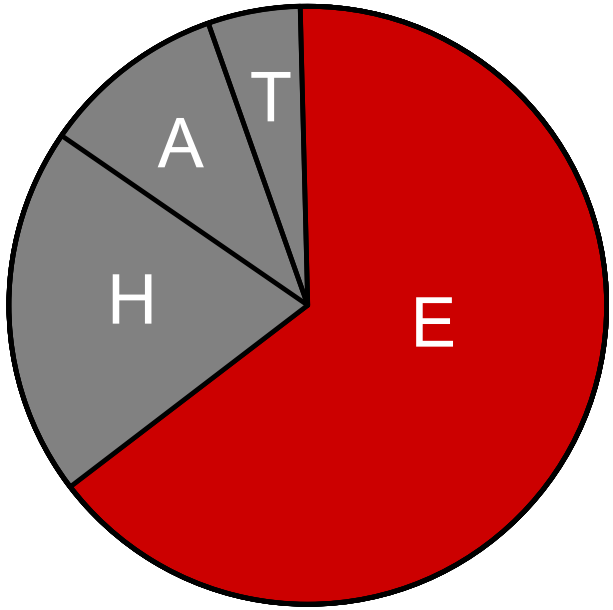
E: Extremity,
H: Head/Neck,
A: Abdomen,
T: Thorax.

Extremities are the most commonly injured part of the body

Injuries



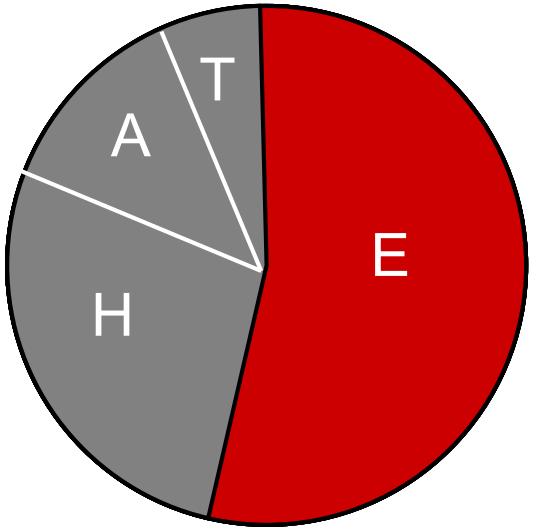
Hospital Costs



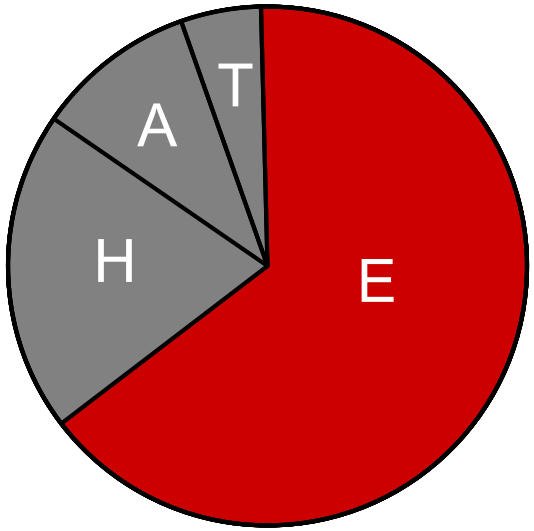
Extremity injury is responsible for most of the hospital costs

J Orthop Trauma 2009 Apr;23(4):261-6.

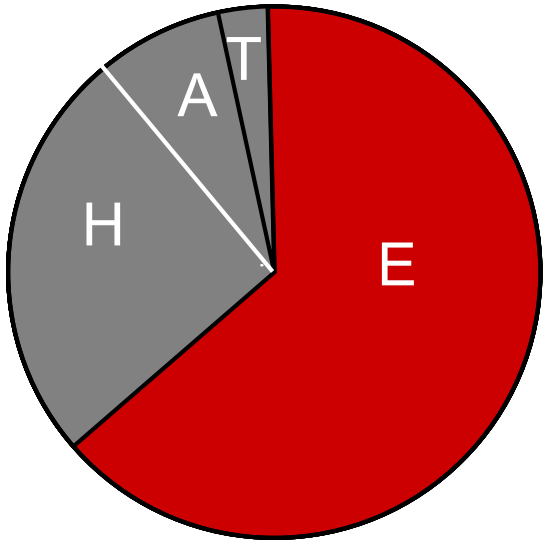
Injuries



Hospital Costs



Disability Costs

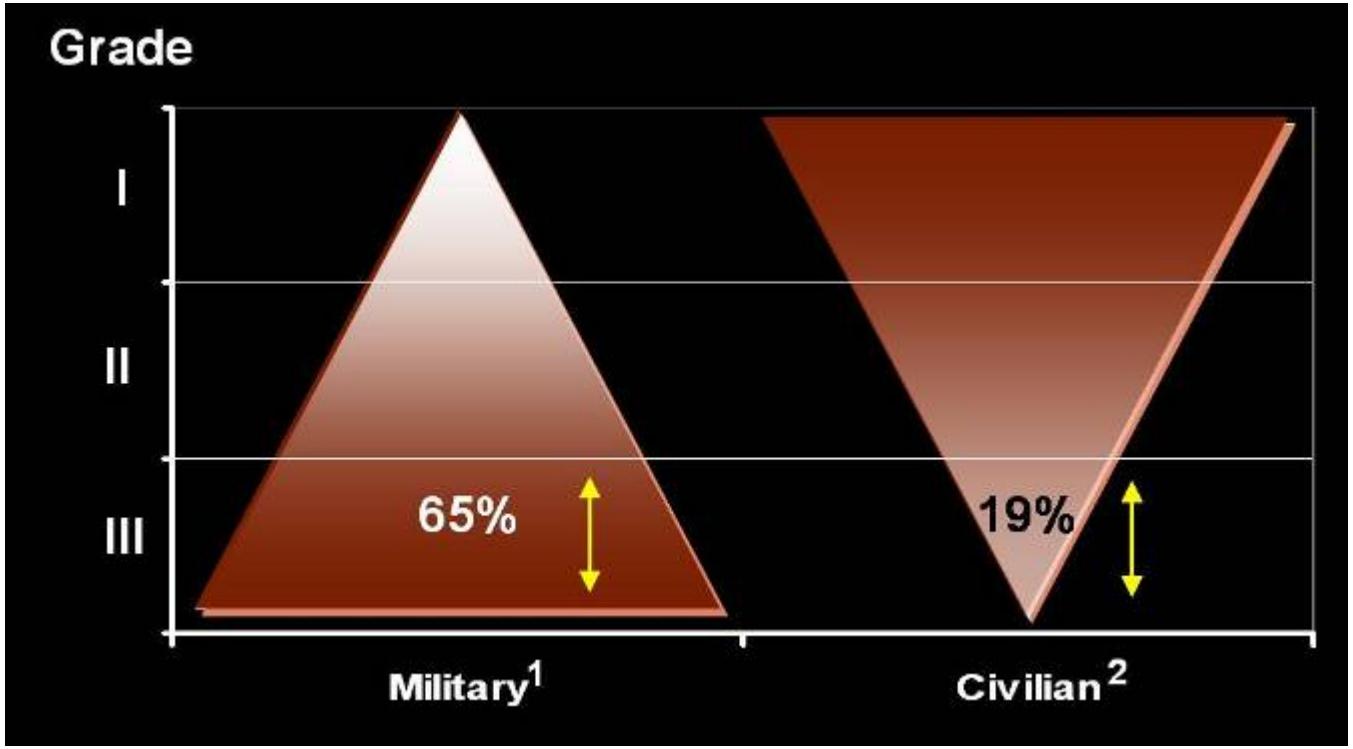


Extremity injury is responsible for most of costs paid to soldiers for disabilities

The money paid out for disability is a good estimate of the amount of morbidity and functional loss of the Soldier

Injury severity relative to civilian medicine

Type III – Either an open segmental fracture, and open fracture with extensive soft-tissue damage, or a traumatic amputation



[1]Johnson, Burns et al. 2007
[2]Gustilo and Anderson 1976

Infectious Complications of Open Type III Tibial Fractures among Combat Casualties

Erica N. Johnson,[1] Travis C. Burns,[2] Roman A. Hayda,[2] Duane R. Hospenthal,[1] and Clinton K. Murray[1]

[1]Infectious Disease Service, Department of Medicine, and [2]Department of Orthopedic Surgery, Brooke Army Medical Center, Fort Sam Houston, Texas

Clinical Infectious Diseases 2007; 45:409-15

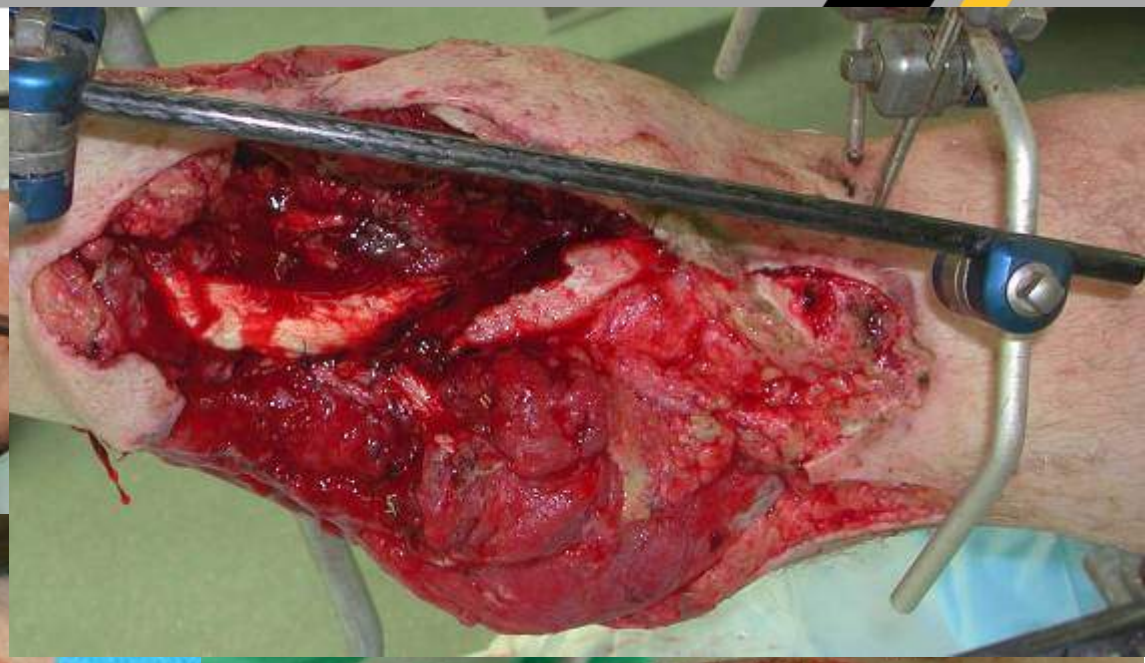
Type III tibial fractures

- All infected
- 37% delayed union associated with infection
- 14% require amputation
  - 80% due to infectious complication

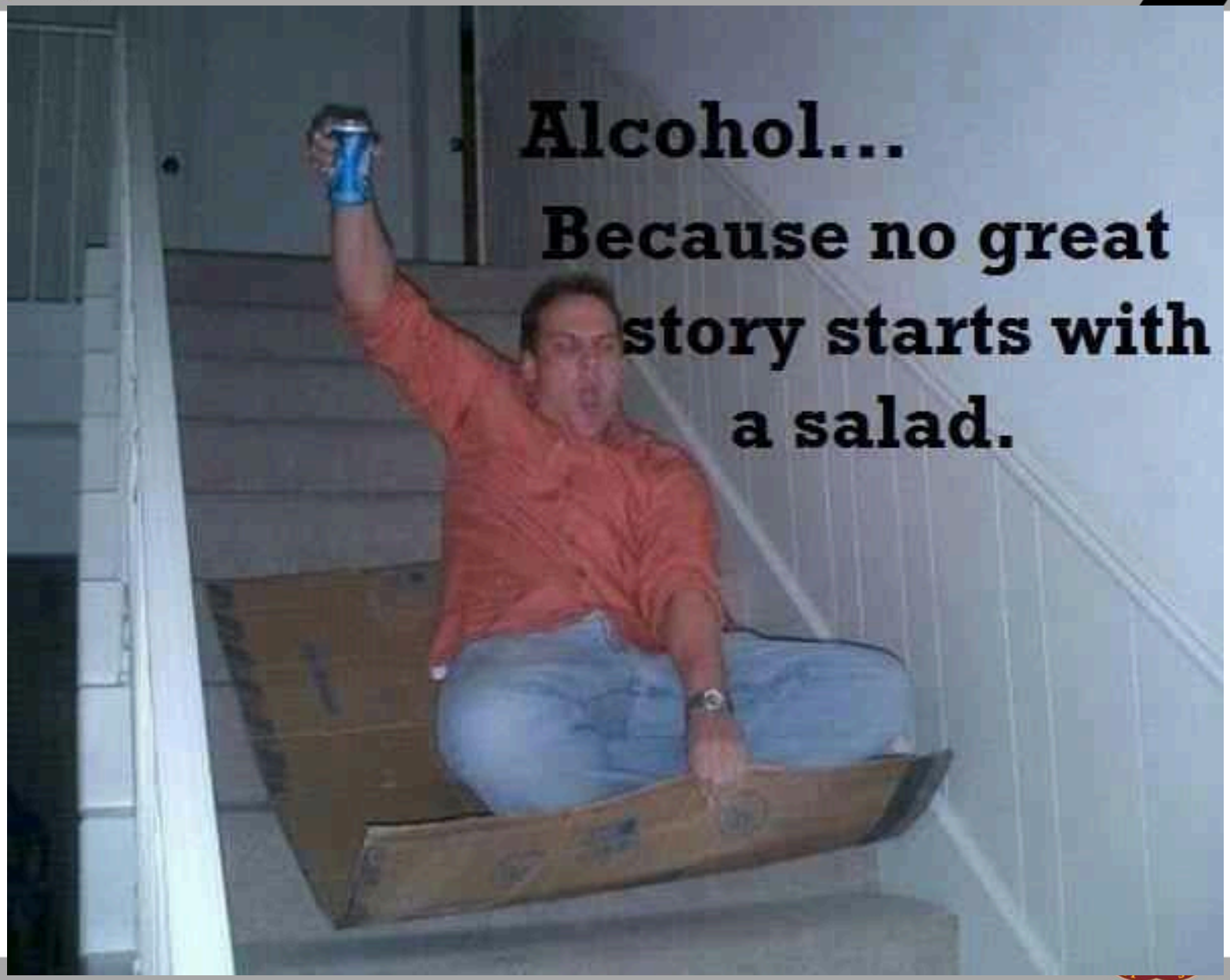
Bottom Line

- Compared to previous wars
  - Likelihood of surviving war wounds has increased
  - Severity of wounds increased
- Multiple wounds-Polytrauma
- Penetrating soft-tissue trauma
- Fractures-Open/Type III
- Infection
- Nonunion
- Nonfunctional residual limbs
  - Volumetric Muscle Loss (VML)

Battlefield Extremity Wounds



Not just a military problem



How can we improve outcomes?

Two of the things we can do to improve outcome of these open fractures:

- **Regenerate the missing tissue**
- **Reduce infection**

Research Areas

Infection

Repair/regeneration of tissue

- -Bone
- -Muscle

Research Areas

Infection

Infection rates of severe open fractures have remained relatively constant for decades

Areas to improve

Timing of antibiotic administration
Irrigation solution
Irrigation device
Timing of debridement
Local antibiotic therapy
Antibiofilm therapy
NPWT
NPWT silver dressings
Augmented NPWT
Implant coatings
Dual purpose bone graft
Biofilm dispersive bone graft

Two different products:

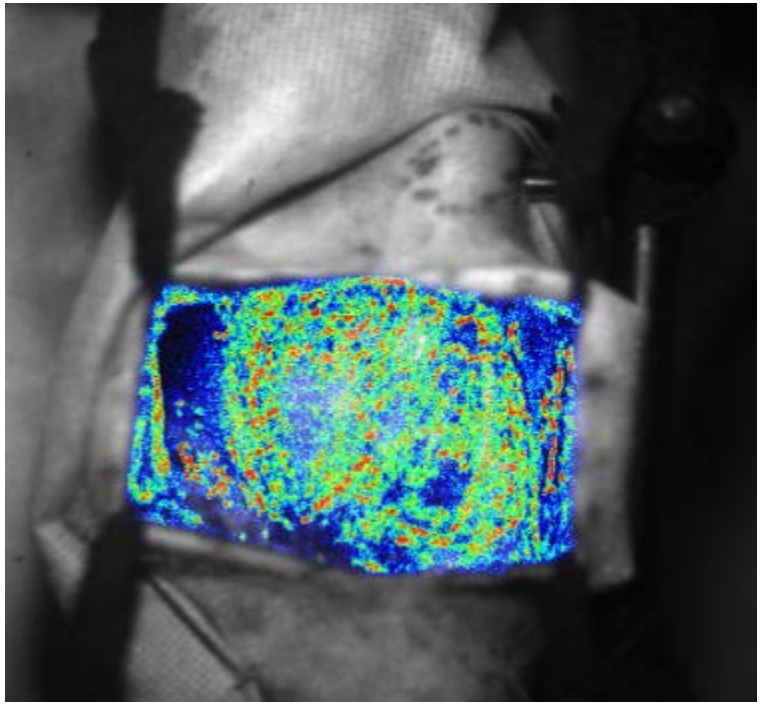
1) Knowledge
2) Materiel

Two different products:

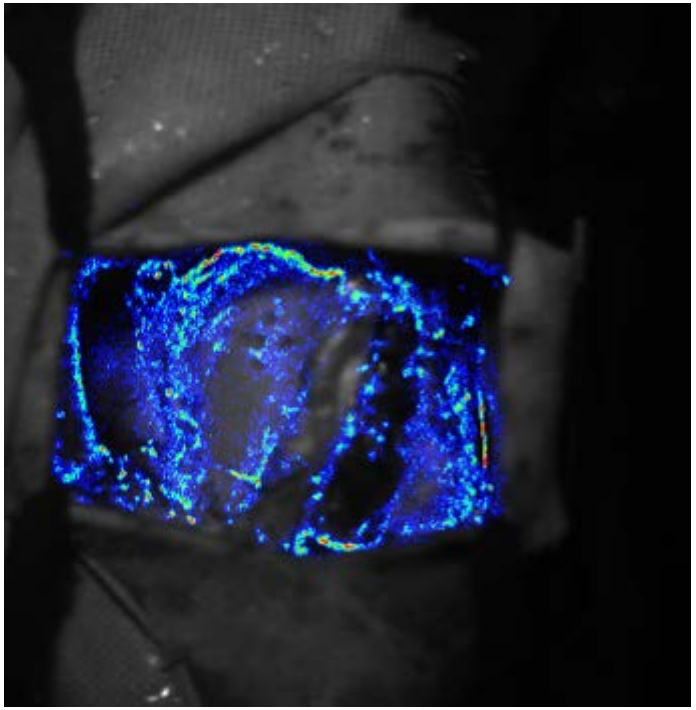
1) Knowledge

2) Materiel

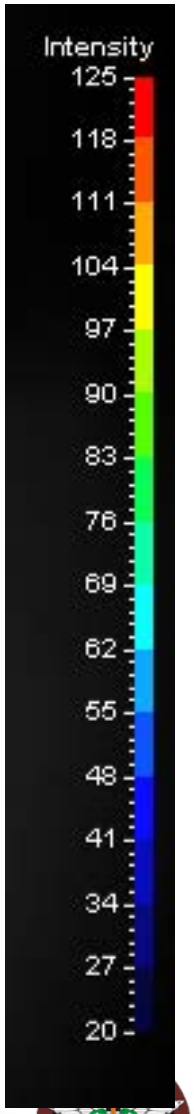
Bioluminescent Imaging

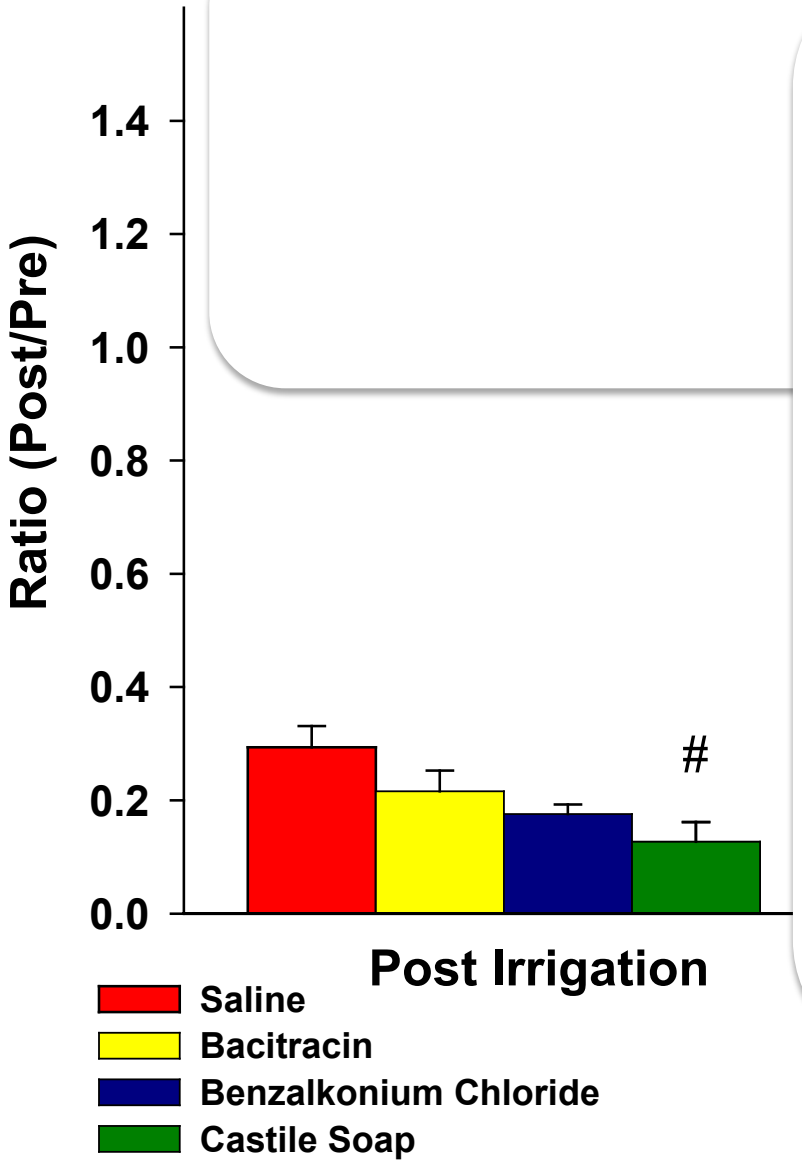


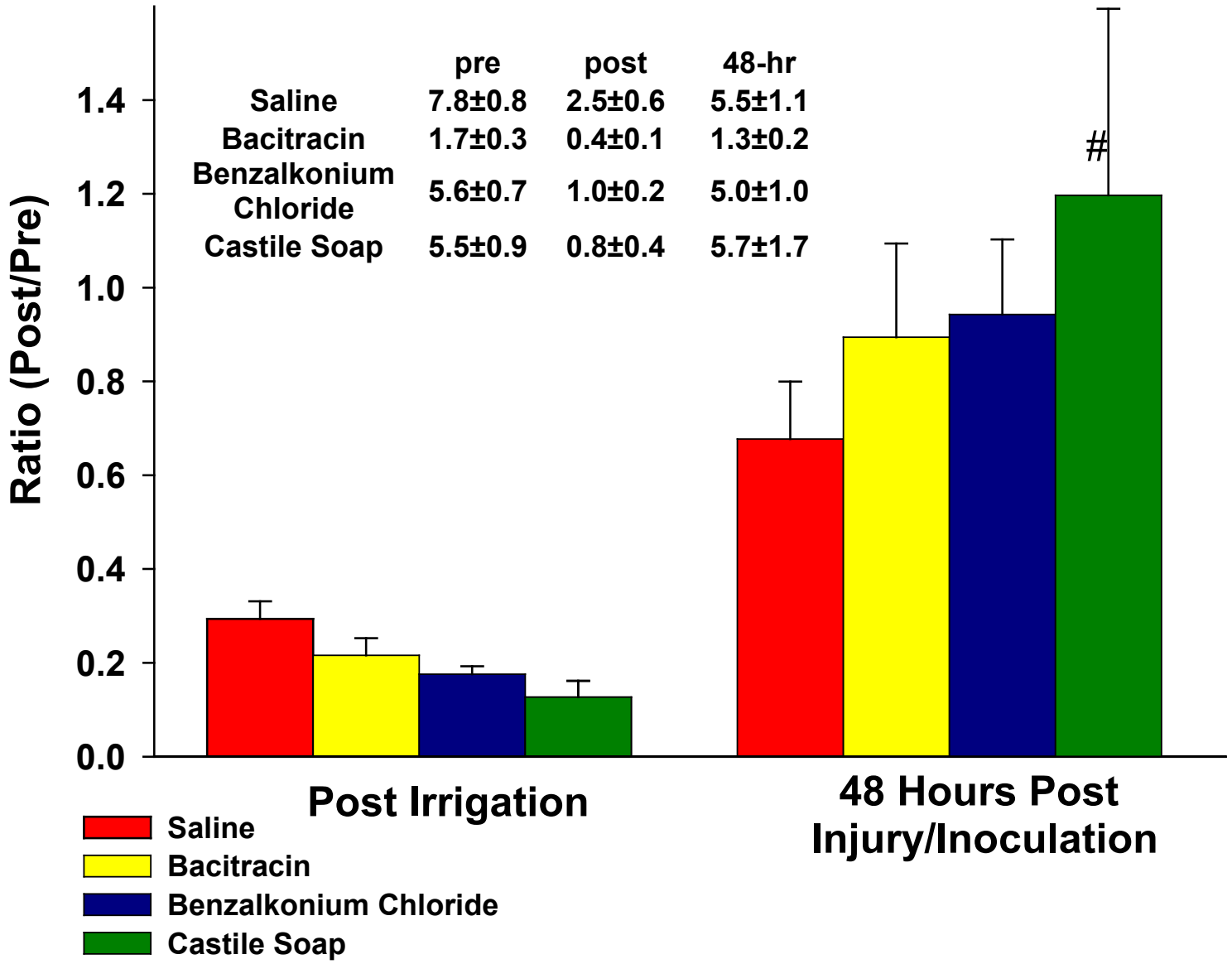
Pre-Irrigation



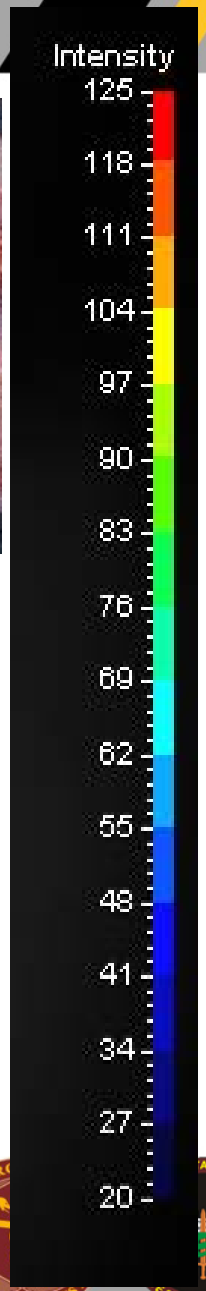
Post-Irrigation



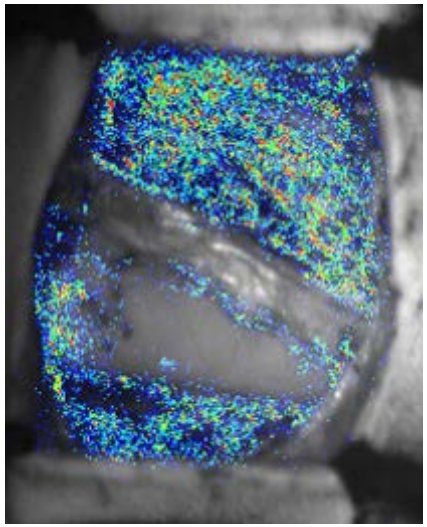

Ratio (Post/Pre)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
#
Post Irrigation
Saline
Bacitracin
Benzalkonium Chloride
Castile Soap

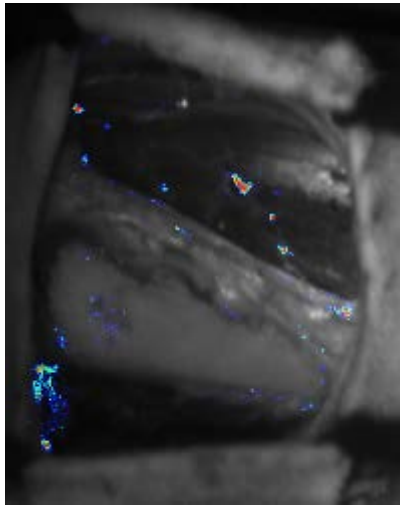

Ratio (Post/Pre)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
pre post 48-hr
Saline 7.8±0.8 2.5±0.6 5.5±1.1
Bacitracin 1.7±0.3 0.4±0.1 1.3±0.2
Benzalkonium Chloride 5.6±0.7 1.0±0.2 5.0±1.0
Castile Soap 5.5±0.9 0.8±0.4 5.7±1.7
#
Post Irrigation
48 Hours Post Injury/Inoculation
Saline
Bacitracin
Benzalkonium Chloride
Castile Soap

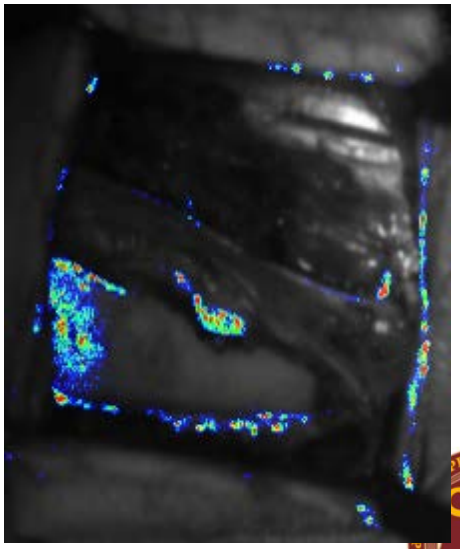
Saline Irrigation



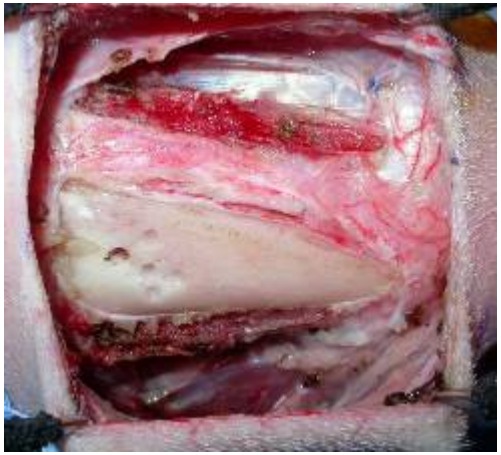
6-Hr Pre-Tx **6-Hr Post-Tx** **48-Hr**







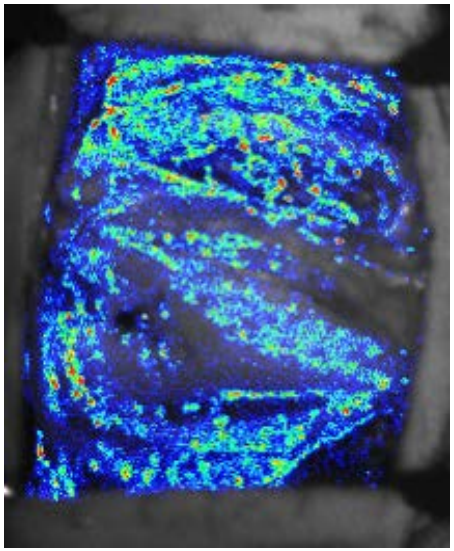
Castile Soap

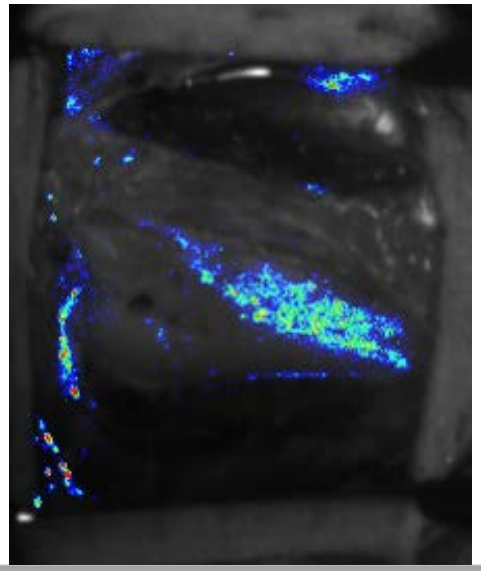


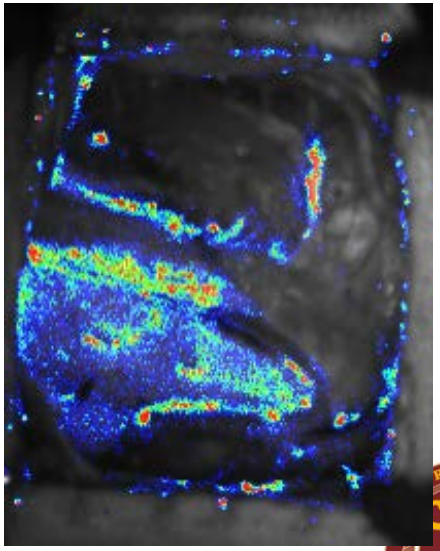
6-Hr Pre-Tx

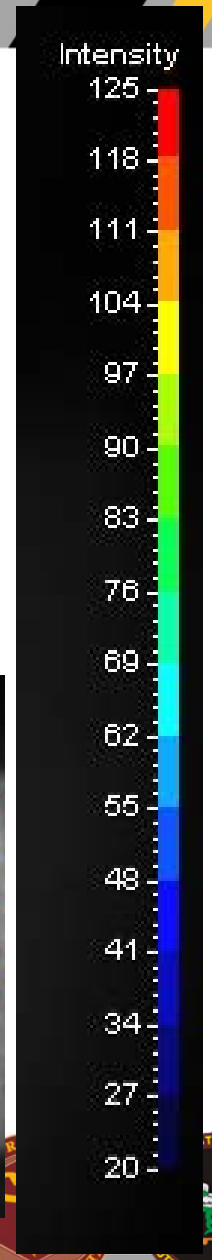
6-Hr Post-Tx

48-Hr



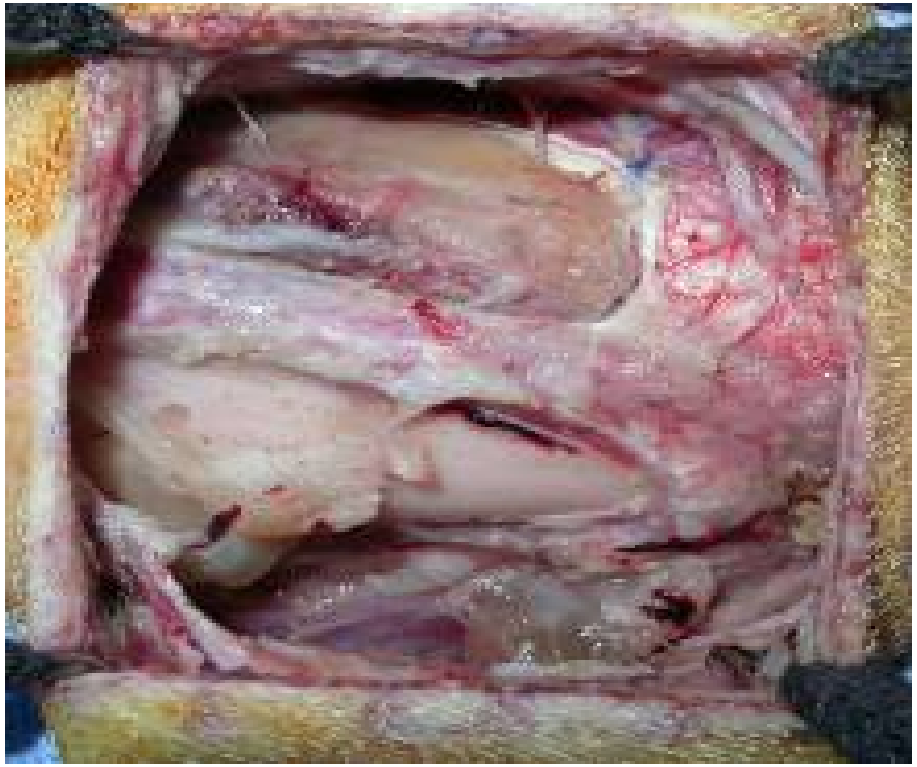






Two days after debridement and irrigation

Saline



Castile Soap

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Trial of Wound Irrigation in the Initial Management of Open Fracture Wounds

The FLOW Investigators*

Table 3. Study End Points for the Comparison of Irrigation Solutions.*

End Point	Soap (N=1229)	Saline (N=1218)	Hazard Ratio (95% CI)	P Value
	number of patients (percent)			
Primary end point: reoperation within 12 mo for infection, wound healing, or bone healing	182 (14.8)	141 (11.6)	1.32 (1.06–1.66)	0.01
Primary end point components				

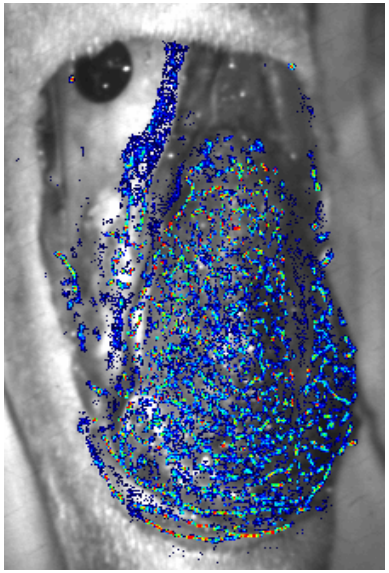
14.8 vs. 11.6%, Hazard ratio of 1.32

Negative Pressure Wound Therapy

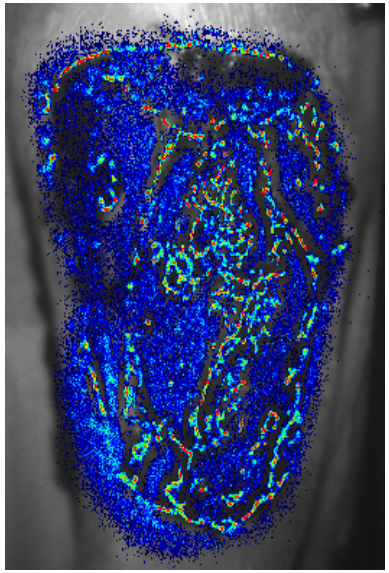
Large Animal Wound Model

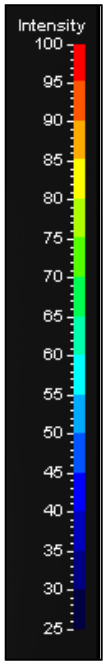
WTD

2 Day



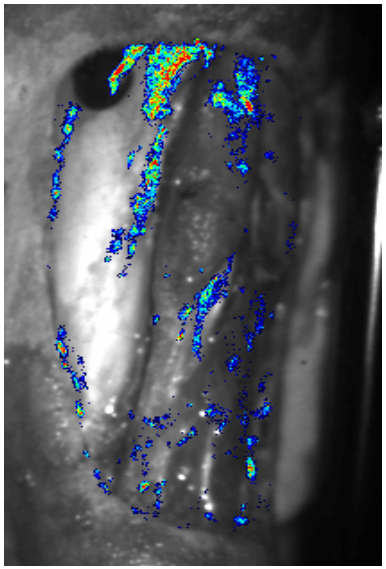
6 Day



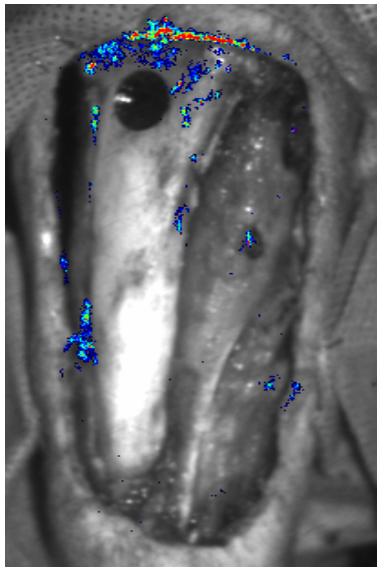


NPWT

2 Day

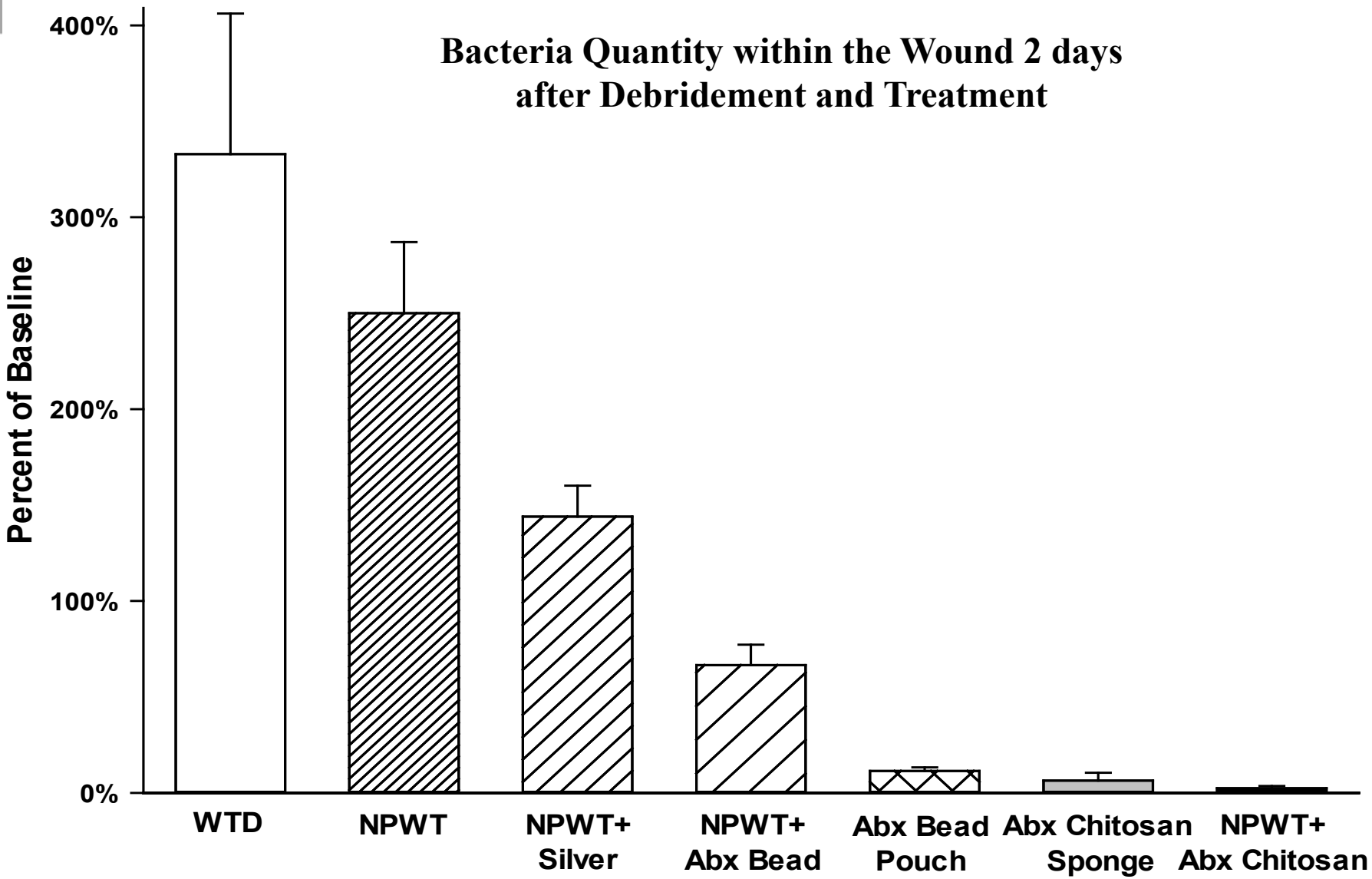


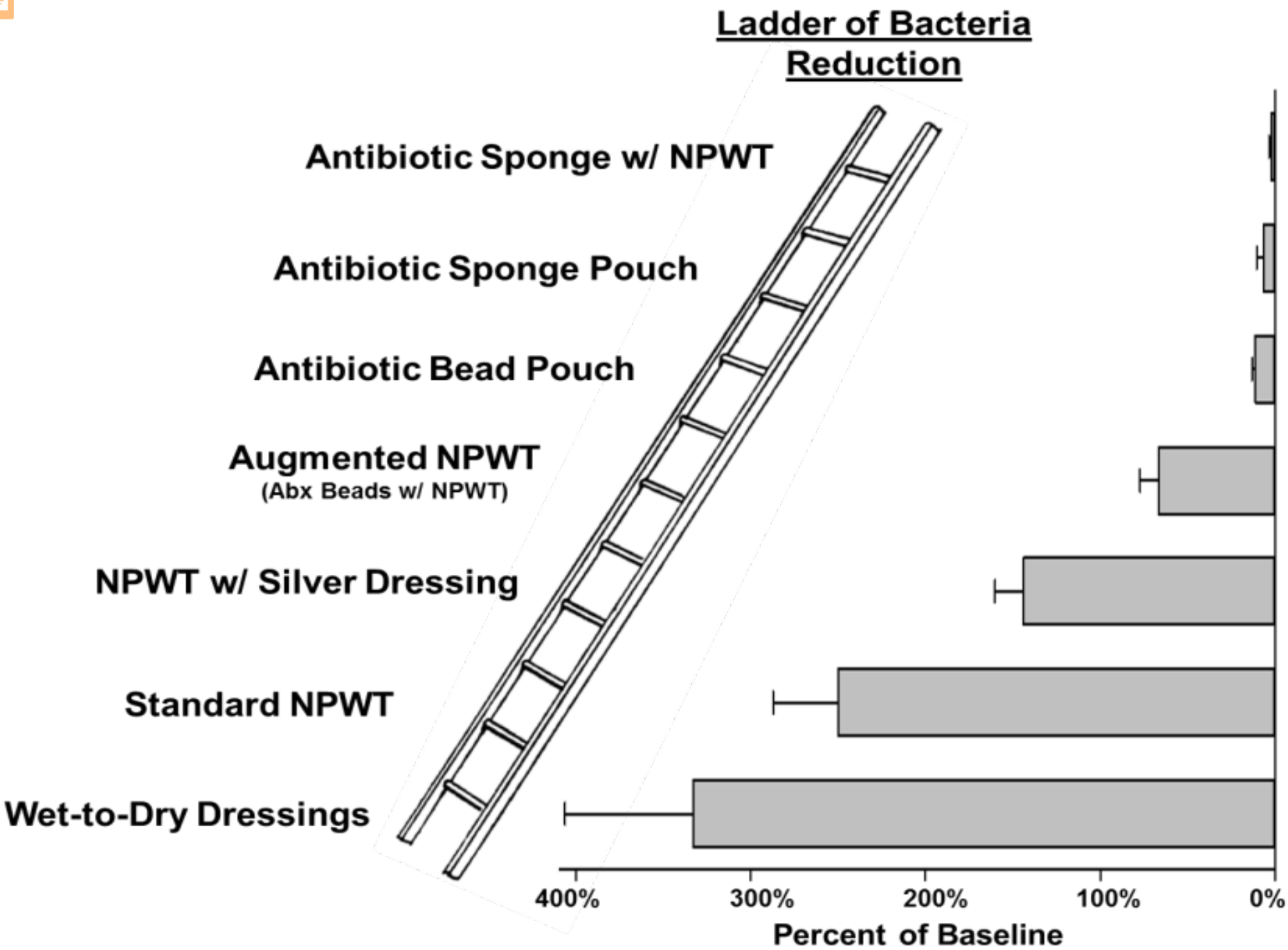
6 Day



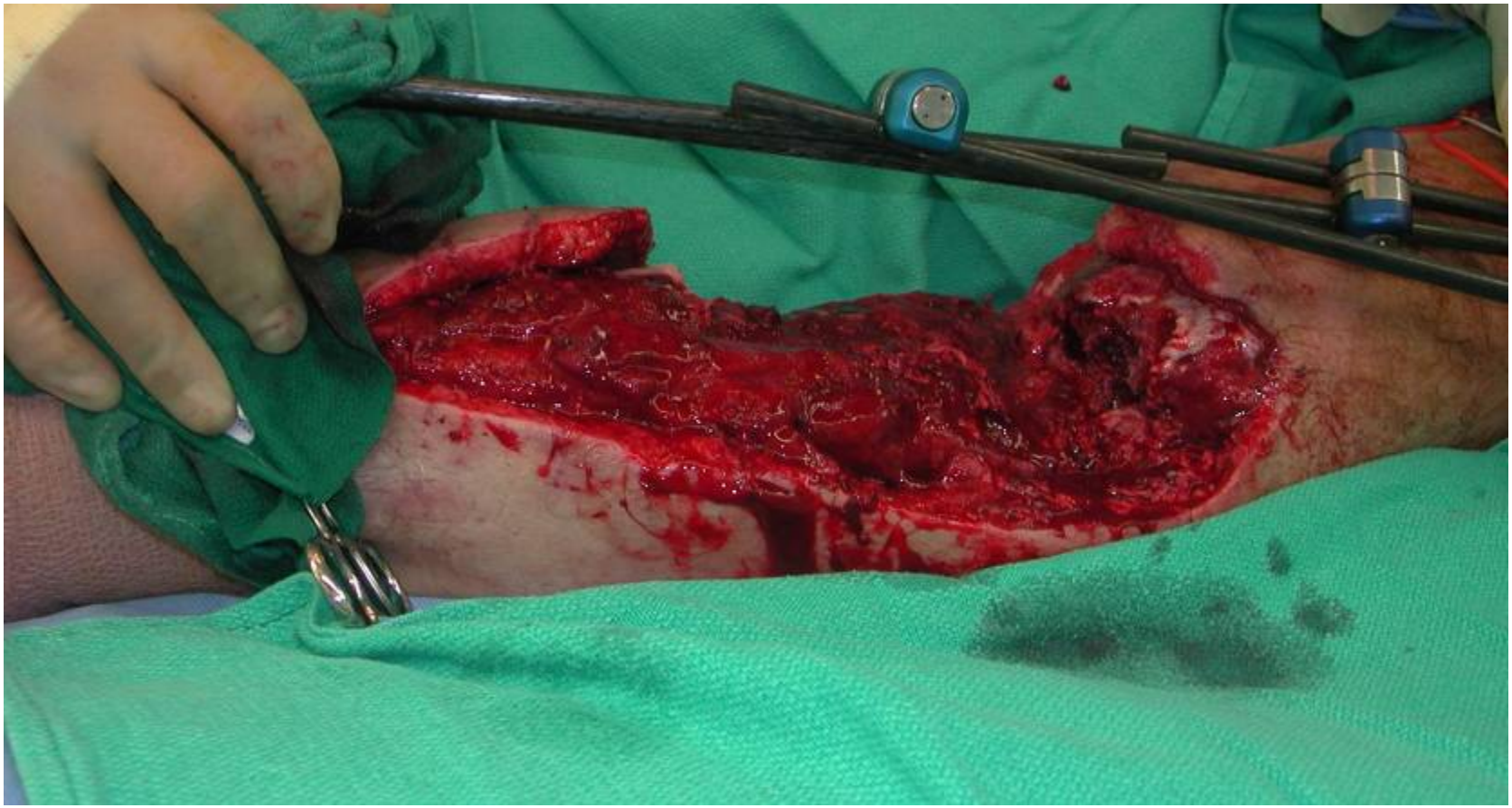
NPWT

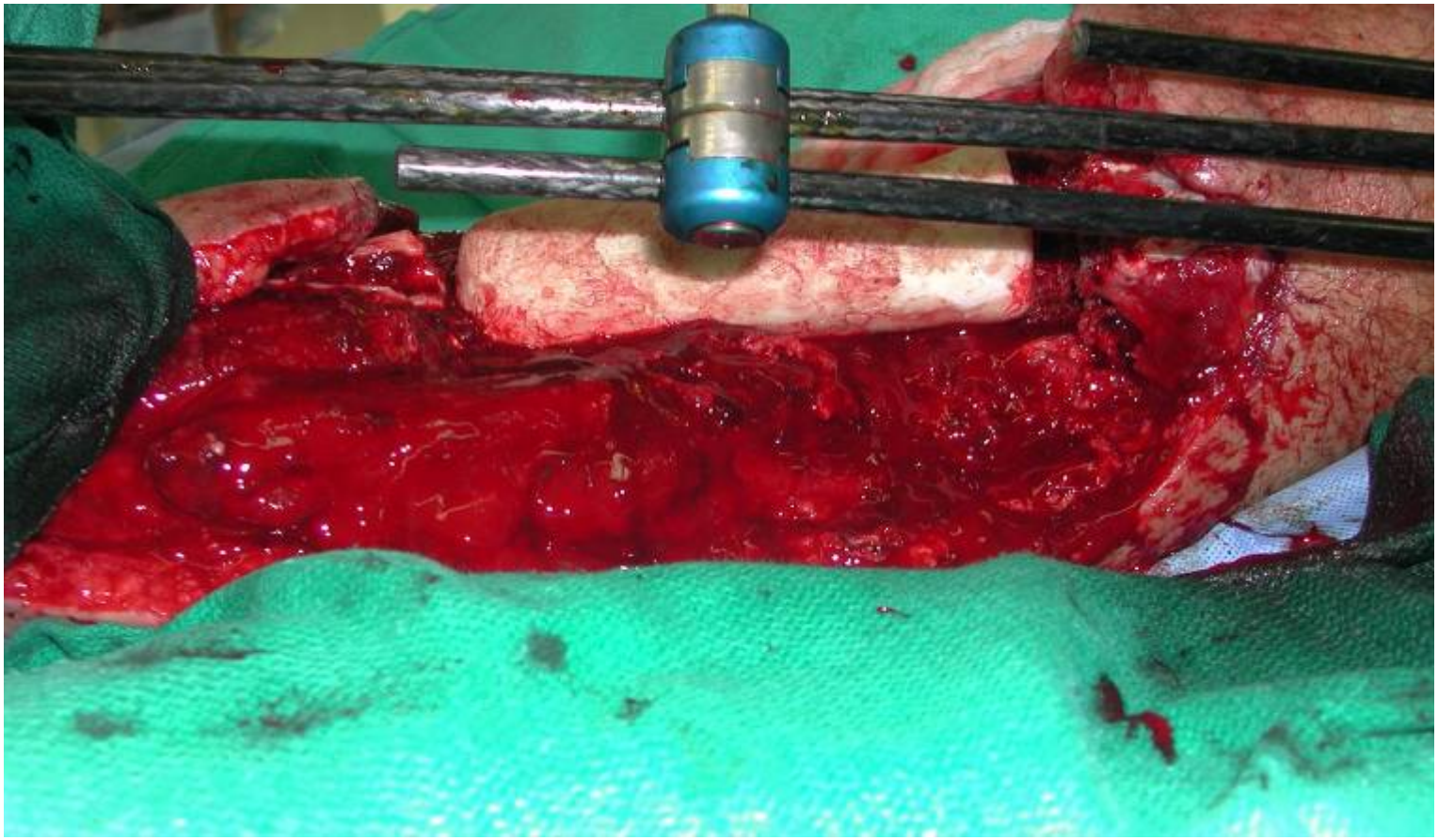
Wet-to-Dry


Bacteria Quantity within the Wound 2 days after Debridement and Treatment
Percent of Baseline
400%
300%
200%
100%
0%
WTD
NPWT
NPWT+ Silver
NPWT+ Abx Bead
Abx Bead Pouch
Abx Chitosan Sponge
NPWT+ Abx Chitosan


Ladder of Bacteria Reduction
Antibiotic Sponge w/ NPWT
Antibiotic Sponge Pouch
Antibiotic Bead Pouch
Augmented NPWT
(Abx Beads w/ NPWT)
NPWT w/ Silver Dressing
Standard NPWT
Wet-to-Dry Dressings
400%
300%
200%
100%
0%
Percent of Baseline

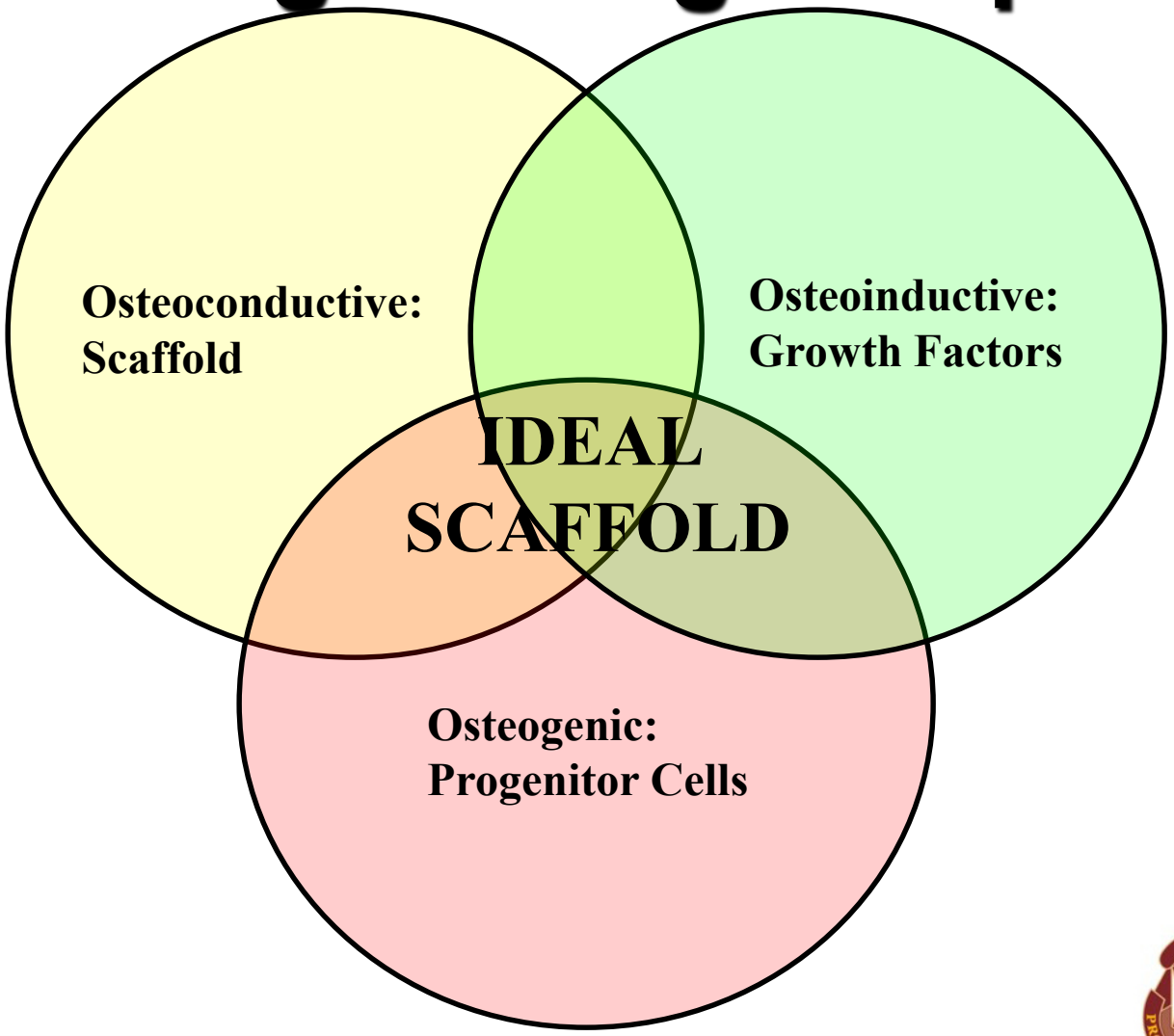
Clinical Vignette



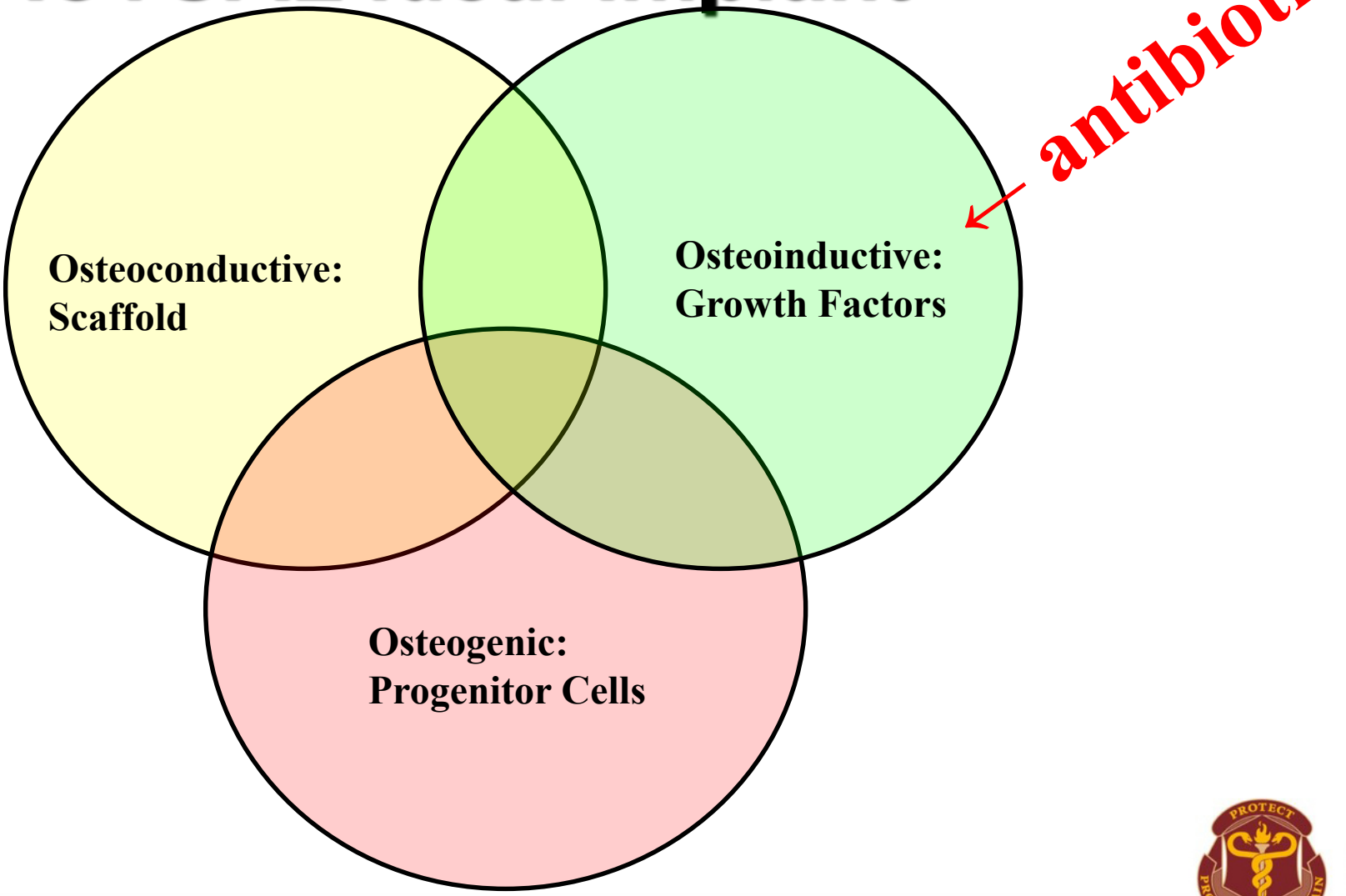


2:43:55 PM
04394320
L
SG

Tissue Engineering Components



ACTUAL Ideal Implant

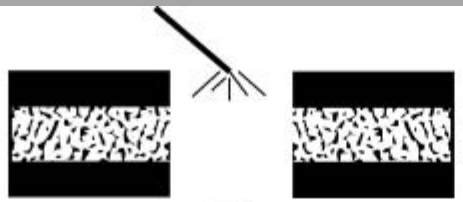


New Strategy to Reduce Complications

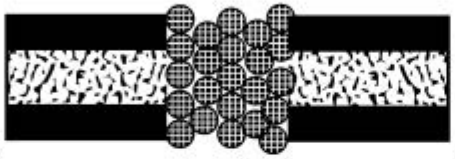
- Protect the graft/implant from colonization until it becomes vascularized

Two different products:

1) Knowledge
2) Materiel

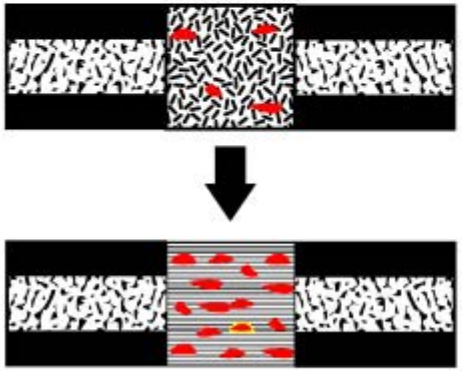


Irrigate, debride, treat with systemic Abx (<5 days)



Treat with local antibiotics (delivery depot, 1 - 3 weeks)

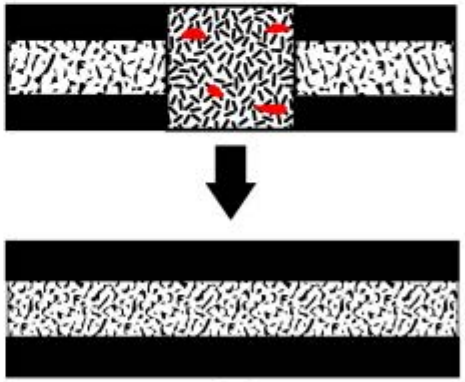
Conventional therapy



Implant conventional graft
Close wound
- No release of antibiotics
- Avascular graft can be nidus for infection
- Bacteria can win the race to the surface

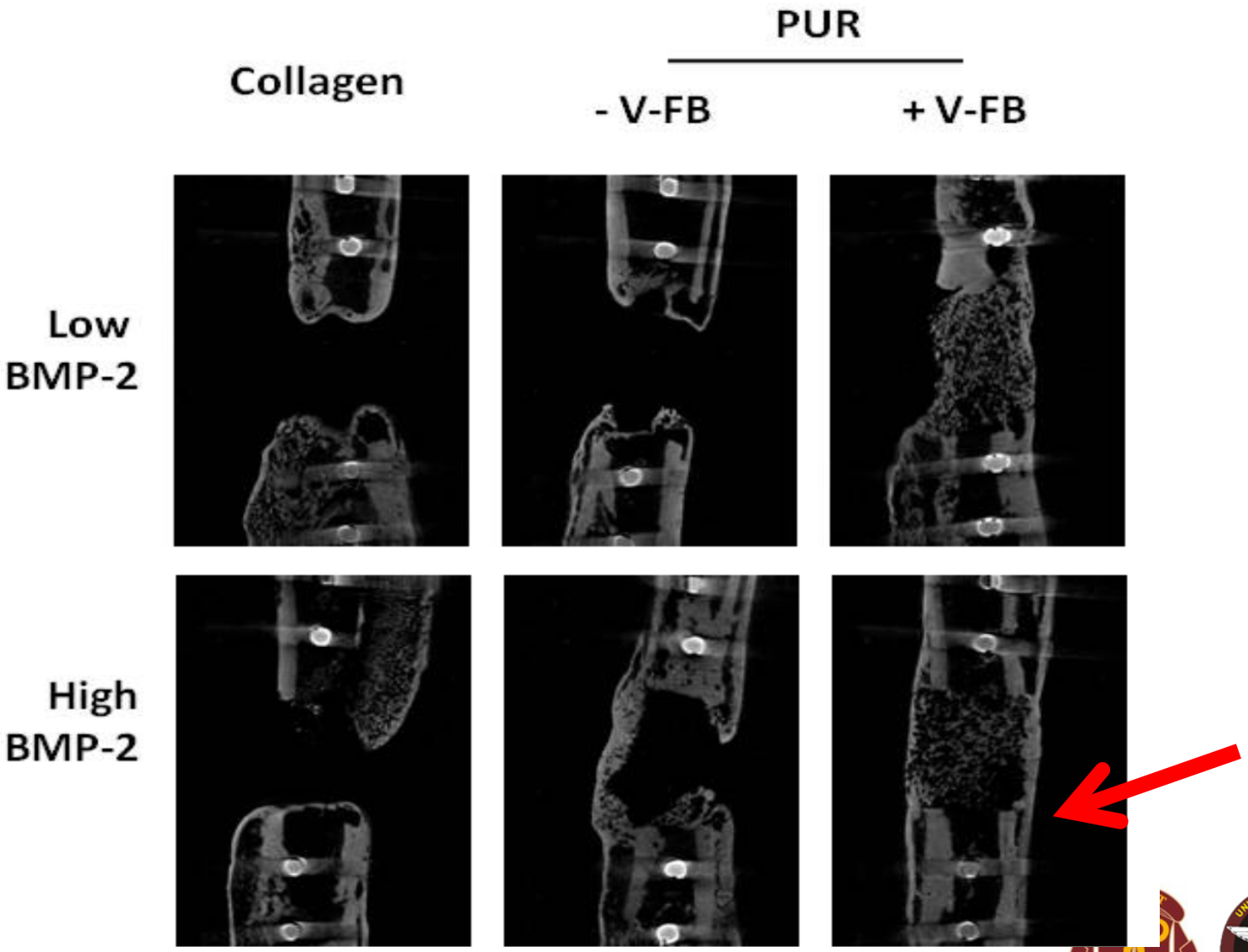
20% incidence of complications (infection, non-union)

Dual-purpose graft



Implant dual-purpose graft
Close wound
- Release antibiotic for >6 weeks to control infection
- Release rhBMP-2 for 2 - 3 weeks to heal bone
- Tissue ingrowth wins the race to the surface

Reduce incidence of infection and non-union


PUR
Collagen
- V-FB
+ V-FB
Low
BMP-2
High
BMP-2

Existing and Emerging Dispersal Agents

D-amino acids (D-AAs)

Cis-2-decenoic acid

Recombinant DNase

Bismuth thiols

Polyamines (Norspermidine)

Statins

Gallium

Auranofin

Research Areas

Infection

Repair/regeneration of tissue

- **Bone**
- Muscle

Research Areas

Infection

Repair/regeneration of tissue

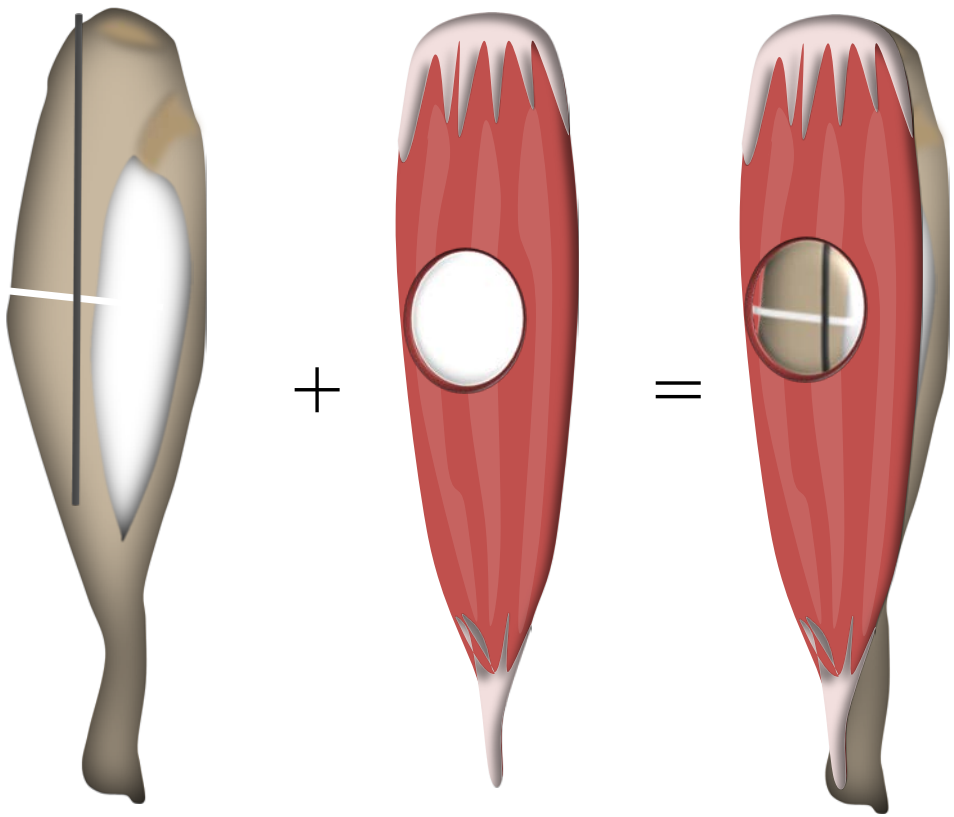
- **Bone (Dysregulated immune response)**
- **Muscle**

Bone-Muscle Composite Injury Model

Male Lewis Rat

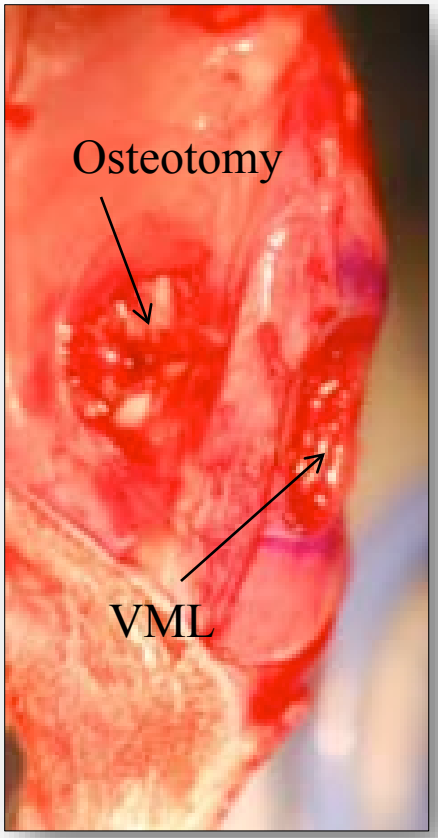
Tibia Osteotomy

Tibialis Anterior VML



Endogenously Healing Bone

Irrecoverable (~20% of Muscle)



Original Article

Severe muscle trauma triggers heightened and prolonged local musculoskeletal inflammation and impairs adjacent tibia fracture healing

B.J. Hurtgen[1†], C.L. Ward[1], K. Garg[1], B.E. Pollot[1], S.M. Goldman[1], T.O. McKinley[2], J.C. Wenke[1], B.T. Corona[1]

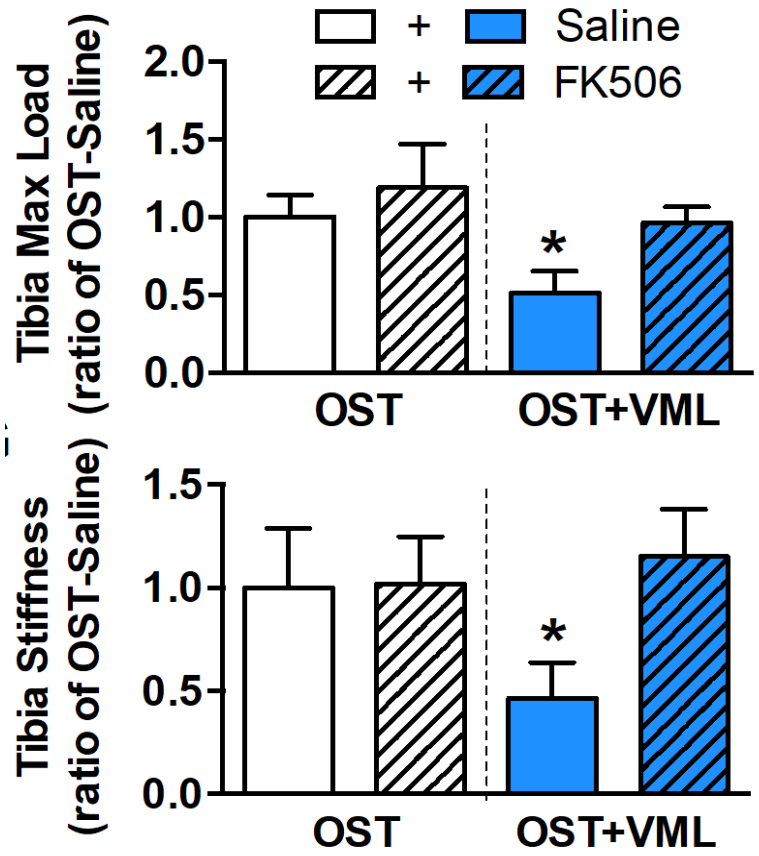
RESEARCH ARTICLE Open Access

Impairment of early fracture healing by skeletal muscle trauma is restored by FK506

Brady J. Hurtgen[1], Beth E. P. Henderson[1], Catherine L. Ward[1], Stephen M. Goldman[1], Koyal Garg[1], Todd O. McKinley[2], Sarah M. Greising[1], Joseph C. Wenke[1] and Benjamin T. Corona[1*]

FK506, also known as tacrolimus, is immunosuppressive; it inhibits T cell proliferation, development, and activation.

Strength of Bone and Muscle at 28d post-injury



FK506 Improved Open Fracture, But Not ***Simple Osteotomy*** Healing

Therapies

- MSCs
- Lipid mediators such as resolvins, maresins, and protectins
- HMGB1 antibodies
- Drugs and small molecules that target the cGAS-STING intracellular pathway

Research Areas

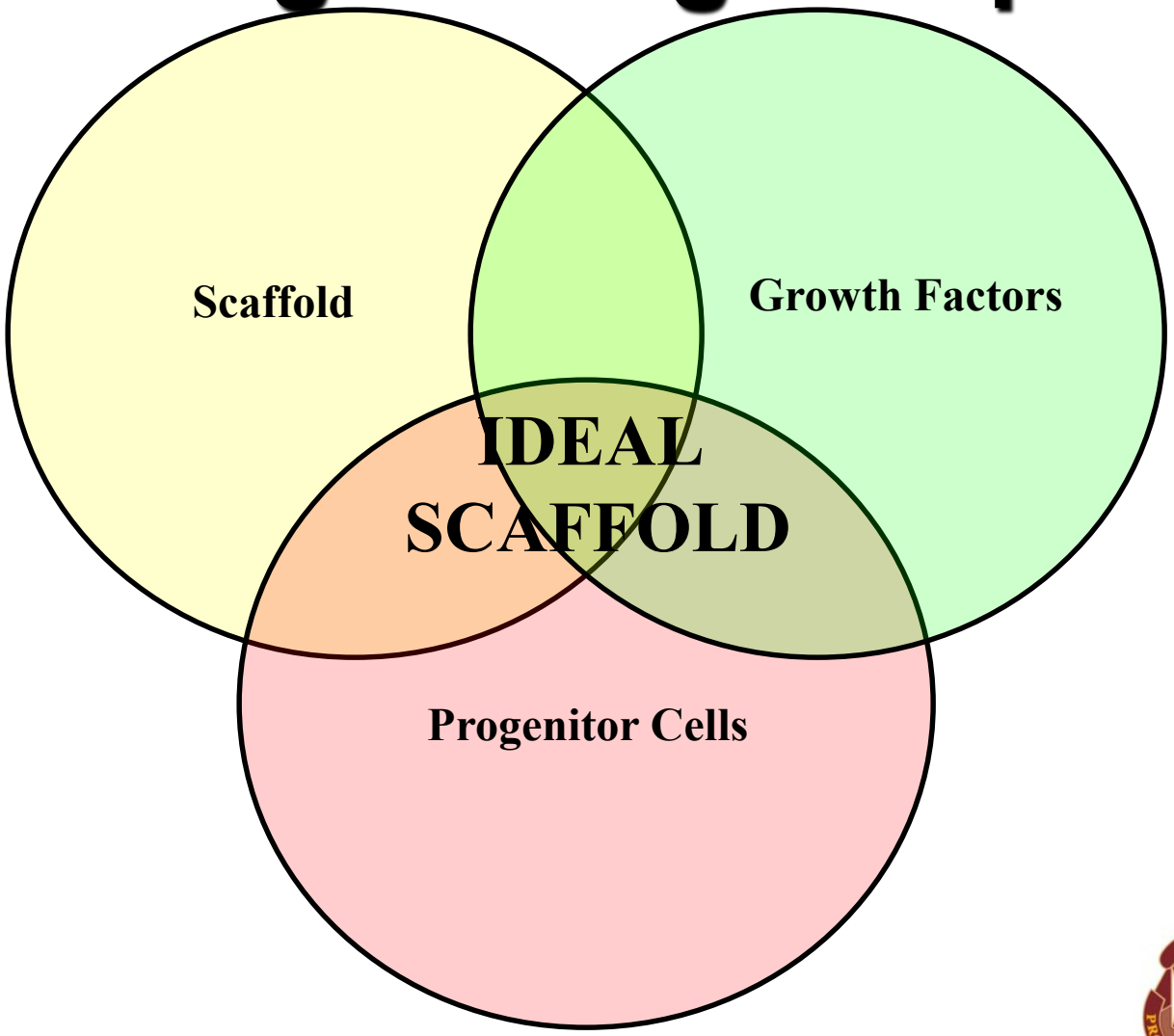
Infection

Repair/regeneration of tissue

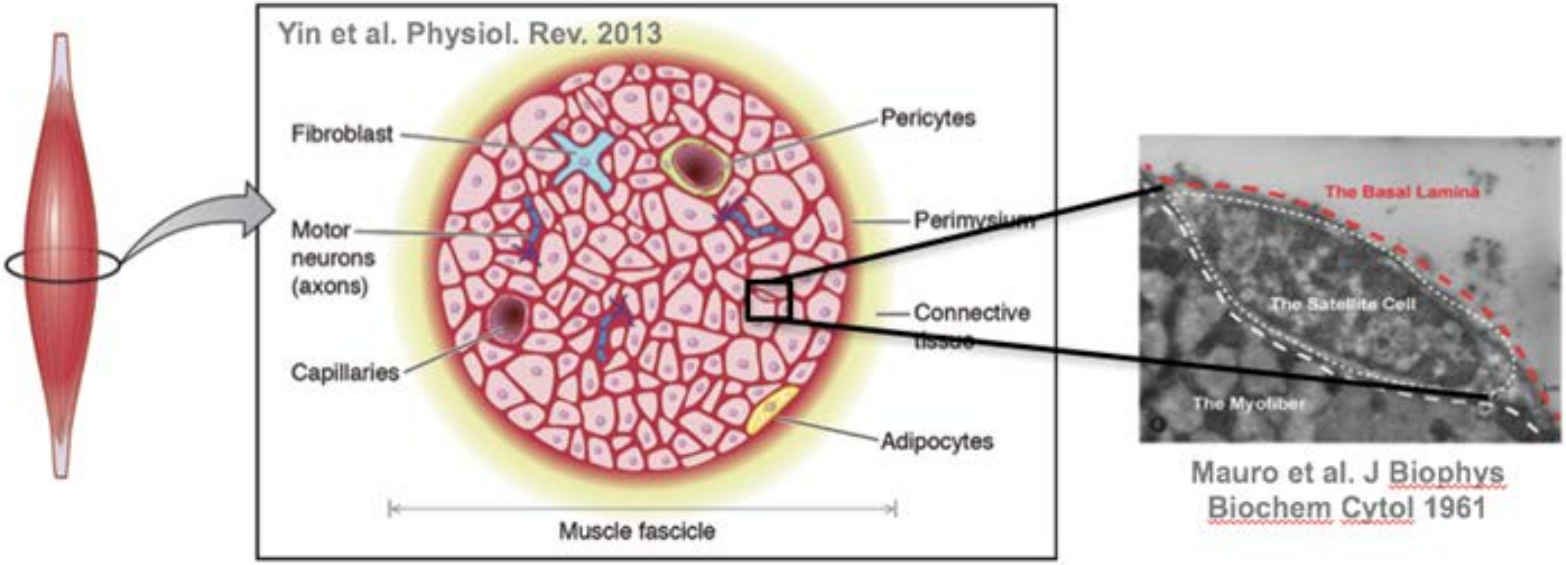
-Bone

-Muscle

Tissue Engineering Components



Satellite Cells



Mauro et al. J Biophys Biochem Cytol 1961

Forecasted Issues

New priority areas with near peer conflicts:

1) Ability for lower extremity injury casualties to remain mobile (exoskeleton)
2) Ability to prevent infections in prehospital setting (topical antibiotics or dressings)
3) Reduce complications and poor outcomes from extended tourniquet applications (cytoprotection, hypometabolism, and anti-apoptosis)

Hemorrhage Control and Resuscitation Research

Michael A Dubick PhD, FCCM, FACN
US Army Institute of Surgical Research
March 28, 2019

Disclaimer

- *The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.*
- Research was conducted in compliance with the Animal Welfare Act, the implementing Animal Welfare Regulations, and the principles of the Guide for the Care and Use of Laboratory Animals, National Research Council. The facility's Institutional Animal Care and Use Committee approved all research conducted in this study. The facility where this research was conducted is fully accredited by AAALAC International.

- *No financial interest in any product mentioned.*

Introduction

- Hemorrhage is the leading cause of death on the battlefield during conventional warfare
- Approximately 24% of the deaths occurring pre-hospital are considered to be potentially survivable, based on expertise from a panel of trauma surgeons
- Of these deaths, over 90% are due to hemorrhage

Introduction

Hemorrhage is leading cause of death from potentially survivable injuries

Task Area Focus:

1) Stop life threatening bleeding by developing measures, drugs, devices and doctrine to control compressible and non-compressible hemorrhage (improve hemostasis), that can be used far forward on the battlefield or at higher echelons of care.

2) Develop far-forward physiologic resuscitation strategies with existing and novel fluids, blood products and drugs that increase circulating volume, improve hemodynamics and hemostasis, and mitigate the secondary consequences of traumatic hemorrhage (immune modulation and metabolic tissue stabilization). Prevent onset or progression of hypothermia

Background

Capability Gaps being addressed:

- Truncal non-compressible hemorrhage is unresolved and incidence of junctional injuries as cause of potentially survivable deaths is increasing

- Hemostatic resuscitation with blood products appears beneficial at Role 3, but there is very limited availability far-forward

- Currently fielded hemostatic dressings have limited efficacy in conditions of coagulopathy (coagulation defects), which is associated with higher mortality rates

- Current resuscitation regimens do not address immune dysfunction or resultant organ failure that develops in survivors

- Uncontrolled hypothermia is associated with higher mortality and prevention remains a capability gap in pre-hospital scenarios

Hemorrhage Control

Combat Gauze (CG)
(gauze + kaolin)

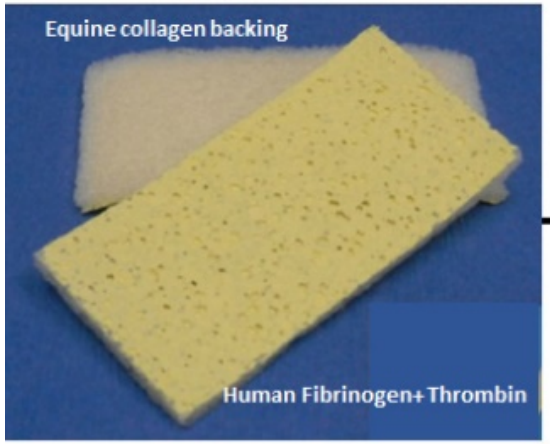
HemCon Bandage (HC)
(chitosan)

Celox Gauze
(chitosan)

Chitogauze
(chitosan)

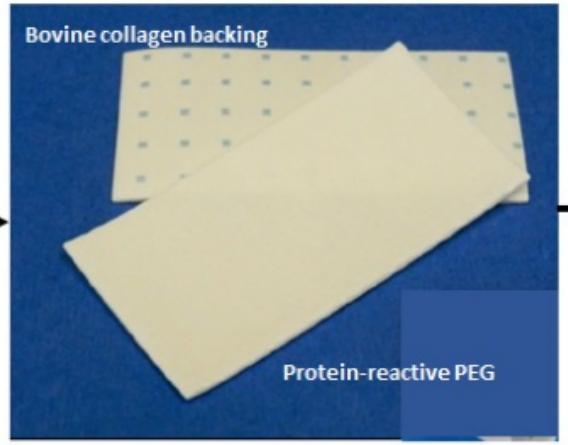
New Hemostatic Dressings

TachoSil



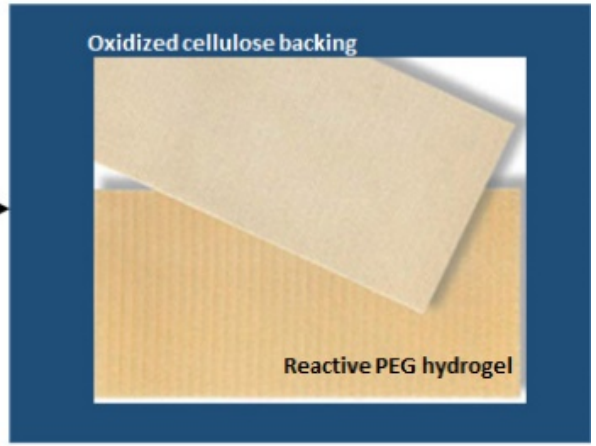
Biological dressing

Hemopatch



Biological+Synthetic dressing

Veriset



Synthetic dressing

New Hemostatic Products

Chitosan Spray Powder

XSTAT Pellets

(Photo courtesy of RevMedX)

Tourniquets

CAT Combat Application Tourniquet

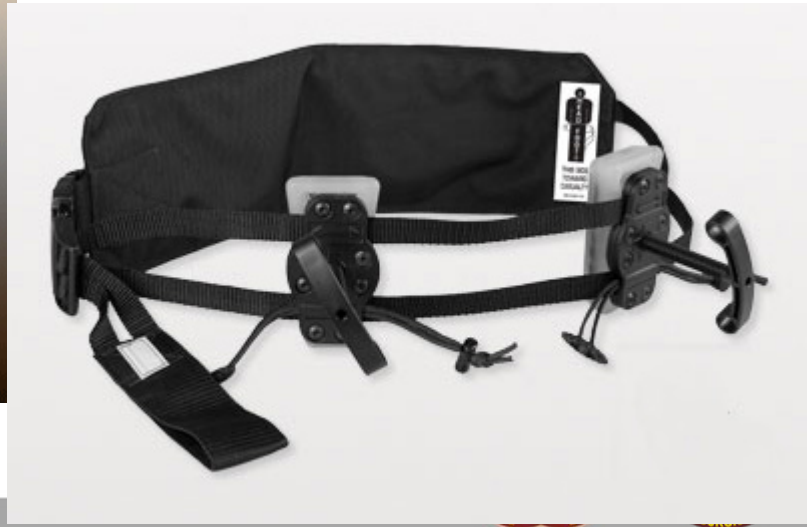
C-A-T™

Junctional Hemorrhage Control Devices

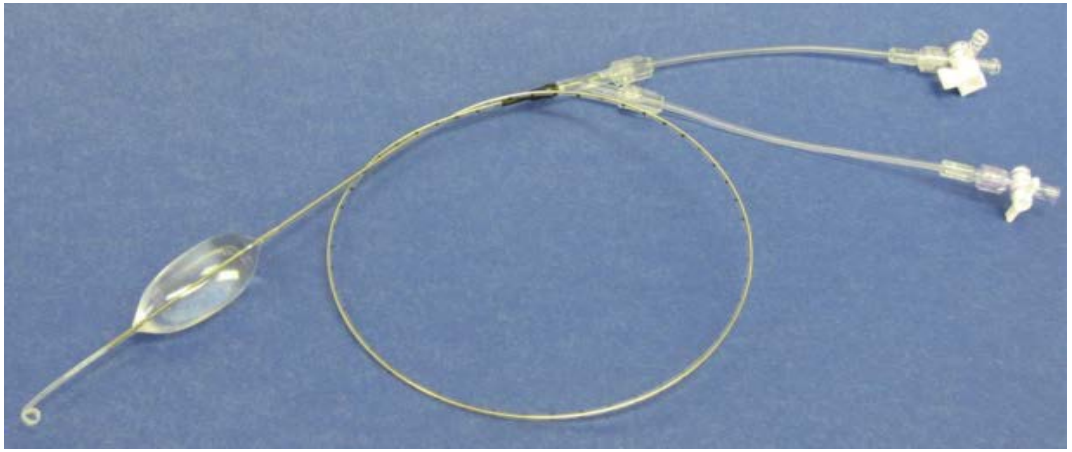
Combat Ready Clamp

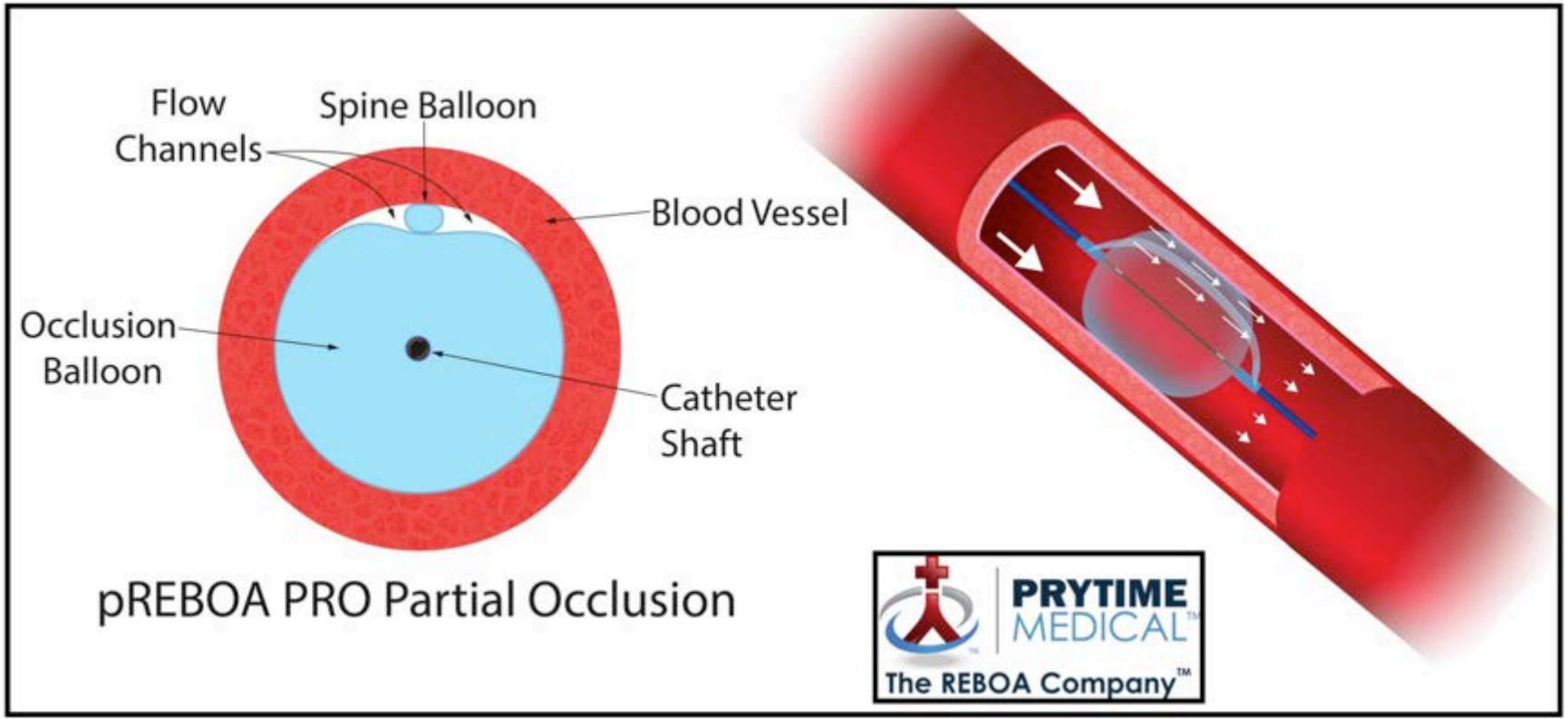
Abdominal Aortic and Junctional TK

Junctional Emergency Treatment Tool



REBOA




Flow Channels
Spine Balloon
Blood Vessel
Occlusion Balloon
Catheter Shaft
pREBOA PRO Partial Occlusion
PRYTIME MEDICAL
The REBOA Company™

Other Hemorrhage Control

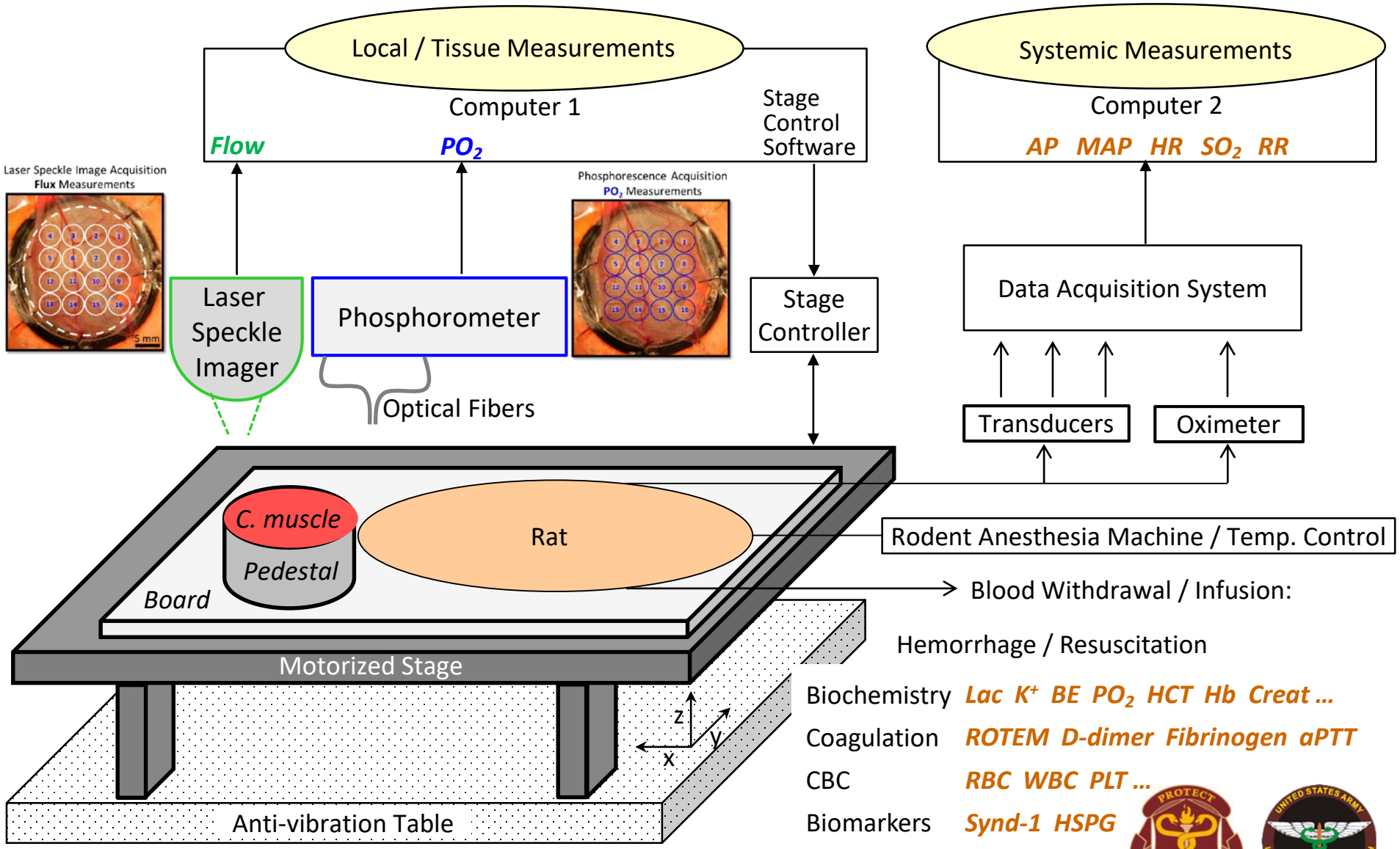
- Expandable gels and foams for internal bleeding (e.g., ResQFoam
- Negative pressure applications
- Clips for hemorrhage control (e.g., iTClamp)

Resuscitation Research

DCR Resuscitation Activities

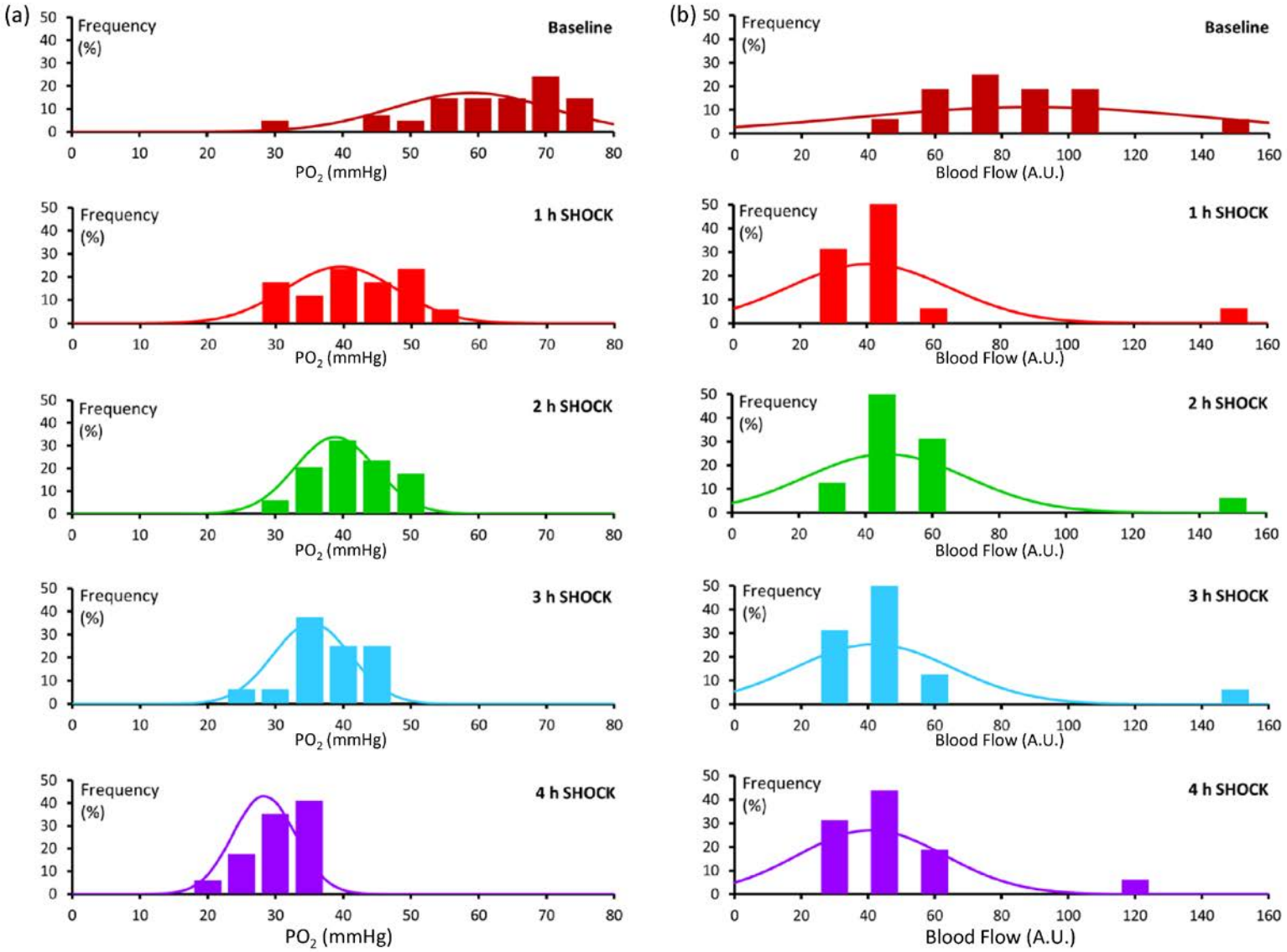
- Blood products (e.g., Plasma, Fibrinogen, Platelets, Blood Product Ratios, Whole blood)
- Other hemostatic drugs - TXA
- Address Metabolic Dysregulation
  - Immune modulators (e.g., Complement inhibitors)
  - Metabolic regulators (e.g, Cytoprotectants, Antioxidants, Metabolic substrates)
- Hypothermia Prevention Devices and Techniques

Flow and Oxygenation in Skeletal Muscle after Trauma and Hemorrhage



Ivo Torres Filho, MD, PhD ivo.p.torresfilho.civ@mail.mil 08/2018

Tissue Oxygenation and Blood Flow



Passive Warming Devices

Wool Blanket

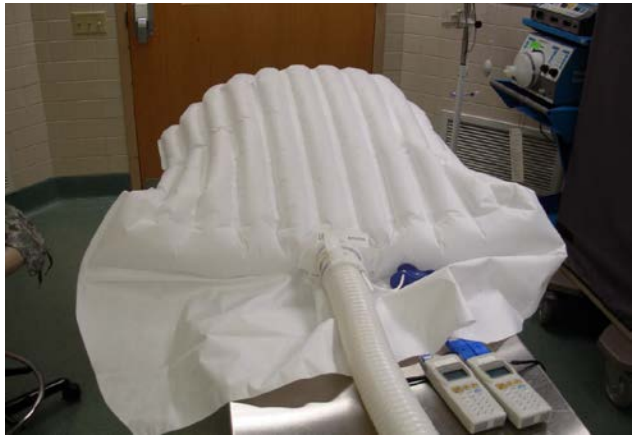
Space Blanket

Blizzard Blanket™

Human Remains Pouch

Active Warming Devices

Original HPMK™



Bair Hugger

Chill Buster

Mini Rescue

Development Pipeline

Current Snapshot of Functional R&D Stages

Discovery-Knowledge
(6.1/6.2/6.3)
Topic Areas
TRL 1-3

- Exploratory models of hemorrhage, burns, and polytrauma
- Biomarkers of fluid resuscitation
- Partial and Next Generation Resuscitative Endovascular Balloon Occlusion of the Aorta (P-REBOA) catheters

Discovery-Product
(6.2/6.3)
Specific Candidate Concepts/Drugs/Devices
TRL 3-4

- Blood products for resuscitation
- Drugs, devices and dressings for hemorrhage control in PFC
- Anti-shock, immunomodulatory drugs
- Stem cell exploratory studies in burn
- Oral resuscitation products

Late Discovery/Transition (6.3)
Pre-clinical & Early Clinical Studies
on Selected Lead Concept/Drug/Device Expected Transition w/in 2 yrs
TRL 4-5

- Oxygen carrier compounds (perfluorocarbon or hemoglobin based) for prolonged field care
- Fibrinogen concentrate
- Ethinyl estradiol- 3-sulfate (SBL)

Full (Clinical) Development
(6.4/6.5)
Specific Product
TRL 5-9

- ResQ Foam (Intracavitary Hemostatic (WSS))
- Tranexamic Acid (TXA)
- REBOA Catheter (Joint with MOST)
- Hemostatic Pellets (XStat)*

*Recent FDA approval

Knowledge Products To Support Clinical Practice

- Prehospital transfusion CPG for damage control resuscitation
- Prolonged field care CPG (hypotensive resuscitation of burn and hemorrhage)
- Best Practices for Use of Tourniquets and Hemostatic Dressings

DCR Contributions to Improved Combat Casualty Care in GWOT

2004 Army Greatest Invention – HemCon Dressing
2005 Army Greatest Invention – Combat Tourniquet
2007 Army Greatest Invention – Damage Control Resuscitation
2008 Army Greatest Invention - Combat Gauze hemostatic Dressing
2009 Army Greatest Invention- Burn Resuscitation Decision Support System

» **Hemostasis Innovations**
- **Tourniquets on the battlefield and in Hospitals**
- **Hemostatic Dressings**

» **Fluid warmers to prevent hypothermia**

» **Hypothermia prevention kit**

» **Intraosseous Infusion Systems**

» **Hextend**

» **Damage Control Resuscitation guidelines**

» **Hypotensive resuscitation guidelines**

- Needle Thoracentesis to treat pneumothorax pre-hospital
  Antibiotics by medics
  Pain control by medics
- Ultrasound to diagnose pneumothorax
- Individual First Aid kit
- Vehicle First Aid kit
- **Fresh Whole Blood**
- **rFVIIa to treat coagulopathic bleeding**
- Wound Irrigation guidelines
- Battlefield burn prevention
  - Safe burning of waste
  - Use of Nomex gloves

Challenges

- Hemostatic dressings that are effective for many hours under Prolonged Field Care scenarios and/or under situations of coagulation dysfunction
- Non-invasive or minimally invasive monitoring/predicting organ dysfunction and blood flow disturbances to tissues associated with hemorrhagic shock
- Defining the success of resuscitation
- All products meeting weight and cube restrictions of military operations

- Many issues faced by the military are similar to those encountered in civilian trauma which typically is a bigger market

Best care is the right device to the right casualty at the right time used in the right way

Thank You

Questions?

Blood Far Forward: technology development for saving lives on the battlefield

U.S. Army Institute of Surgical Research
James A. Bynum, PhD, Deputy Chief, Coagulation and Blood Research
james.bynum.civ@mail.mil
28 March 2019

Disclaimer

Disclaimer:

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Departments of the Army, Air Force or the Department of Defense.

Disclosures:

The authors have no relevant conflicts of interest.

Coagulation & Blood Research

- Department Mission
  - Blood products for the battlefield
  - Diagnosis & management of Acute Traumatic Coagulopathy (ATC)
  - Treatment of shock
- Capability Gap(s) addressed by research
  - Resuscitation of hemorrhage, #1 cause of preventable death on the battlefield
- Scientific Thrust Areas
  - Platelet & Whole Blood storage
  - ATC diagnostic device
  - ATC therapeutic bundle
  - Shock therapeutic bundle
  - Cellular therapeutics

Blood & Blood Products

Development Pipeline – Current Snapshot of Functional R&D Stages

Discovery-Knowledge (6.1/6.2/6.3)
Topic Areas
TRL 1-3

- Mechanisms of Coagulopathy
- Mechanisms of Blood Product Function
- Mechanisms of Blood Storage Lesions
- Metabolic lesions in shock

Discovery-Product (6.2/6.3)
Specific Candidate Concepts/Drugs/Devices
TRL 3-4

- Whole Blood/Platelet Preservation
- Novel Drugs & Diagnostics for Coagulopathy Intervention
- Synthetic Blood Products (HBOC, eng. plasma)
- Shock therapeutics
- Cell therapy products for trauma & radiation injury

Late Discovery/Transition (6.3)
Pre-clinical & Early Clinical Studies
on Selected Lead Concept/Drug/Device Expected Transition w/in 2 yrs
TRL 4-5

- Efficacy Studies of Whole Blood, Platelets, HBOC, eng. Plasma, shock therapeutics, cell therapy
- Shelf Life Studies (Whole Blood and Components)
- Additives and Preservatives
- Diagnostics for coagulopathy management

Full (Clinical) Development (6.4/6.5)
Specific Product
TRL 5-9

- Diagnostic device characterization (TEG, ROTEM, Coagulex, etc.)
- Blood warming/cooling devices
- Spray-dried SD Plasma
- Platelet-derived Hemostatic Agent
- Lyophilized Plasma
- Extended-Life Red Cells*
- Cryopreserved Platelets
- Whole Blood Pathogen Reduction Technology (WBPRT)
- Tranexamic acid
- LTOWB

Knowledge Products To Support Clinical Practice

- Walking Blood Bank CPG
- CPGs for Transfusion/DCR
- Blood Use Guidelines
- Anticoagulation & blood management for ECLS

Go/no go decision gates

anthony.e.pusateri.civ@mail.mil

Unclassified

US Military Death Distribution (2001-2011)

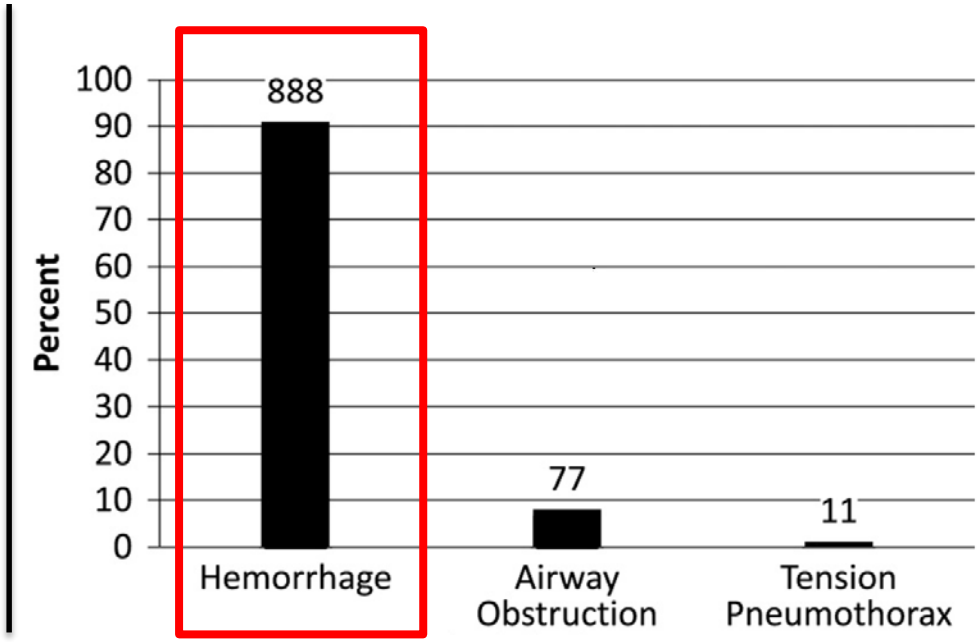
4,596 Combat Deaths

Died of Wounds (≥ Role II)
580 deaths

Killed in Action (Role I)
4,016 deaths
- 3,040 nonsurvivable
- **976 potentially survivable**

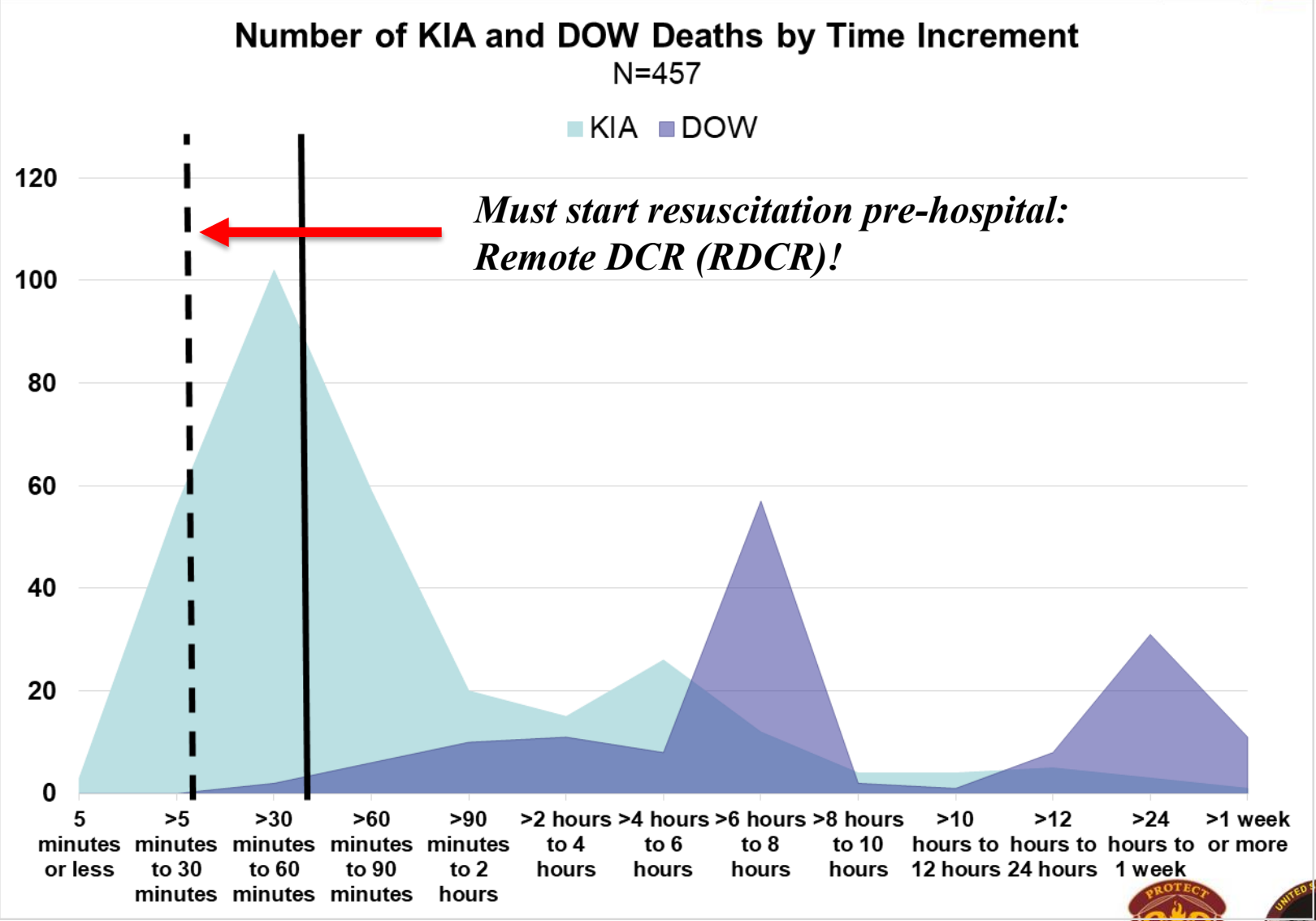
Eastridge. J Trauma Acute Care Surg. 2012

Potentially Survivable Deaths - 976 (24.5%)



BLEEDING IS THE PROBLEM!

Time to Death: KIA/DOW
"Golden Hour" is too late to start DCR…



Shackelford, et al.
JTS 2016.

Pre-hospital blood transfusion → Large reduction in risk of death

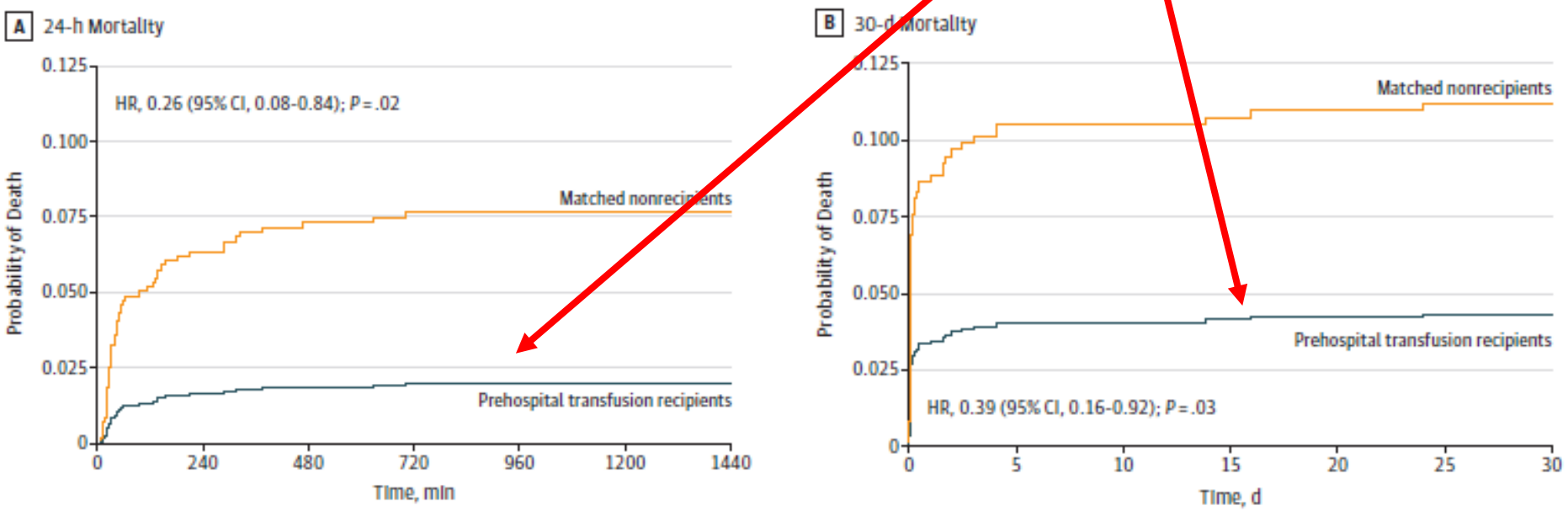
JAMA | Original Investigation

Association of Prehospital Blood Product Transfusion During Medical Evacuation of Combat Casualties in Afghanistan With Acute and 30-Day Survival

Stacy A. Shackelford, MD; Deborah J. del Junco, PhD; Nicole Powell-Dunford, MD; Edward L. Mazuchowski, MD, PhD; Jeffrey T. Howard, PhD; Russ S. Kotwal, MD, MPH; Jennifer Gurney, MD; Frank K. Butler Jr, MD; Kirby Gross, MD; Zsolt T. Stockinger, MD

Which curve do you want to be on?
-- I'll take lower probability of death!

Figure 3. Mortality of Prehospital Transfusion Recipients vs Matched Nonrecipients



Start transfusion here if not sooner!

So, what is DCR?

- Hemorrhage and injury cause **acute blood failure** or **hemovascular dysfunction**.
- **DCR treats drivers of blood failure simultaneously with blood (and TXA).**
- DCR is most effective if **started immediately**.
- Risk-benefit of products should be considered in light of exsanguination mortality.
- Simplicity is a virtue: **LTOWB**.
- Use **cold platelets***: longer shelf life, stop bleeding.

** cold platelets from apheresis or… in WB*

Give BLOOD for (R)DCR

LTOWB is the simplest way to deliver the functionality of lost patient blood.

The freshest WB is the most functional.

BUT: most available data on improved outcomes with pre-hospital transfusion based on COMPONENTS!

ANY mix of WB or components is better than clear fluid.

4°C

R&D Priorities for WB

- **WB collection kit**
- **New WB anticoagulant/storage solution (CPDA-1 approved 1978!!)**
- Determine blood storage acceptability parameters under **field conditions** (e.g., "red lines" for temperature excursions)
- NATO **"uni-card"** for ABO/Rh, HIV, HBV, HCV rapid diagnostics
  - 4 different tests currently!
  - Very cumbersome
  - Results available in <5min to >30min

Cold chain is still a challenge!

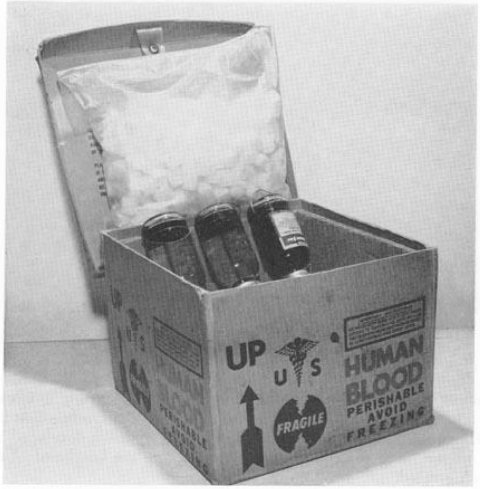


FIGURE 185.—Refrigerated container, developed at Fort Totten after Korean War and still in use (1962). Note ice in plastic container in cover.

Shipment & inventory tracking part of Commander's Critical Information (not "just medical" – must integrate with C3 systems)

Better containers
Wireless temperature monitoring
Inventory tracking (RFID, GPS, etc.)

The Medic: bring blood to the fight?

GHB: 7lbs tare, **10lbs loaded**, 2L/**4U** payload volume,
Can maintain payload at 1-10C for 72-90hrs

An extra 10lbs for 4U!

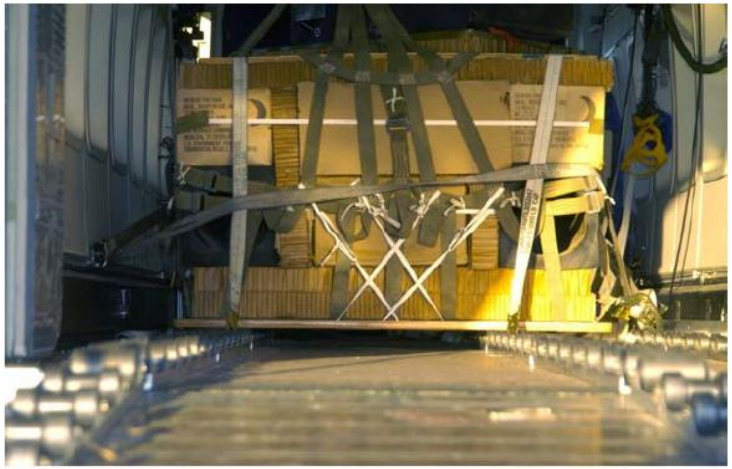
Need cooling to condition GHB panels…

Sometimes you have to travel light

Universal WB
4°C stored

VS.

Blood delivery: from air drop to drones



R&D Priorities for FDP, TXA

- » **FDP** field-compatible container (**plastic**) & **increased production capacity** (only France, Germany & South Africa; US coming soon)
- » **More convenient TXA** dosing, administration

RDCR Supporting Diagnostics

- **RDCR diagnostic test**: Hg, lac, PT/INR, "compensatory reserve monitor"
  - Need triage tool, "brakes vs. gas" guidance

Streamline!

Current devices either don't do enough or are too bulky and require cold chain for reagents or lag physiology (lactate).

Lactate

Blood Glucose

RDCR Supporting Diagnostics

- » **"Compensatory reserve monitor"** based on arterial waveform analysis very promising
  - » performed well in early clinical studies

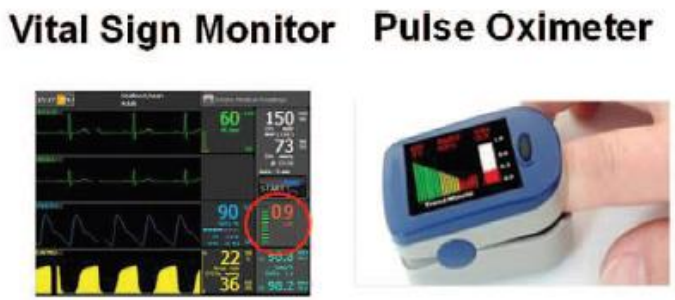


FIG. 14. Examples of the CRI integrated on a current medical monitor (left photo) and on a simple pulse oximeter (right photo).

Results available immediately, no blood draw or reagents, dynamic

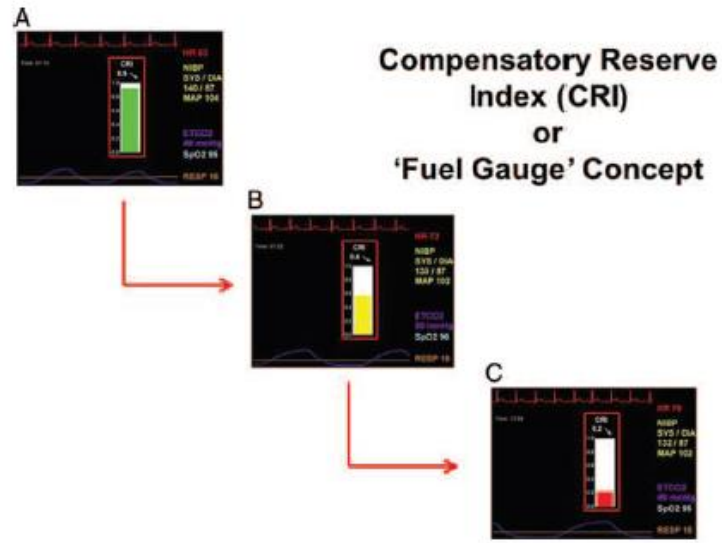


FIG. 10. A monitor screen illustrating the progression in the compensatory reserve index (CRI) "Fuel Gauge" from "green" (1.0–0.6, (A)) to "amber" (0.6–0.3, (B)) to "red" (0.3–0.0, (C)). Modified from Van Sickle et al. (30).

THE COMPENSATORY RESERVE FOR EARLY AND ACCURATE PREDICTION OF HEMODYNAMIC COMPROMISE: A REVIEW OF THE UNDERLYING PHYSIOLOGY

Victor A. Convertino,* Michael D. Wirt,* John F. Glenn,† and Brian C. Lein†

*U.S. Army Institute of Surgical Research, JBSA Fort Sam Houston, Texas; and †U.S. Army Medical Research and Materiel Command, Fort Detrick, Maryland

SHOCK, Vol. 45, No. 6, pp. 580–590, 2016

More RDCR and WB research opportunities

Hypotensive resuscitation = hemostatic procedure, not optimal treatment

→ How long can you go hypotensive with WB (or components)?

→ How high can you bring BP without popping clot?

Hemostatic performance limits of stored WB

→ CPD to 21d vs. CPDA to 35d vs. components

→ WFWB added to stored: optimal ratio (3:1, 4:1, components?)

→ Leukoreduction, pathogen reduction, etc. effects?

→ New storage solution?

→ Better blood warmers for pre-hospital?

LTOWB

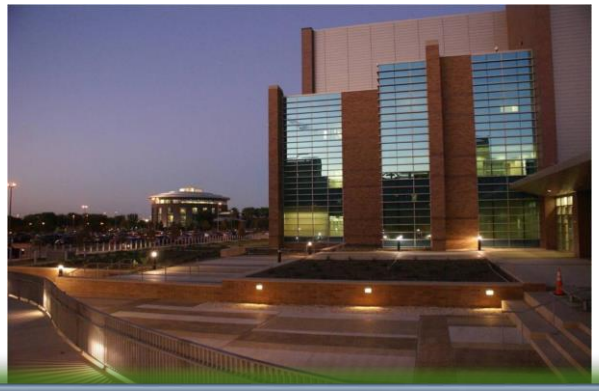
→ Best titer methodology vs. antibody removal?

Prolonged Field Care

→ Can you "stretch" WB with albumin, fibrinogen, PCC?

Coagulation & Blood Research

- Principle Investigators
  - COL Andre Cap, MD, PhD
  - James Bynum, PhD
  - Dan Darlington, PhD
  - Adam Meledeo, PhD
  - Xiaowu Wu, MS, MD
  - Kristin Reddoch-Cardenas, PhD
  - Maryanne Herzig, PhD
  - Barbara Christy, PhD
  - Patrick Ketter, PhD
  - Prajeeda Nair, PhD
  - Andrew Meyer, MS, MD



Battlefield Health And Trauma Research

LTOWB

Cold Platelets

Questions?

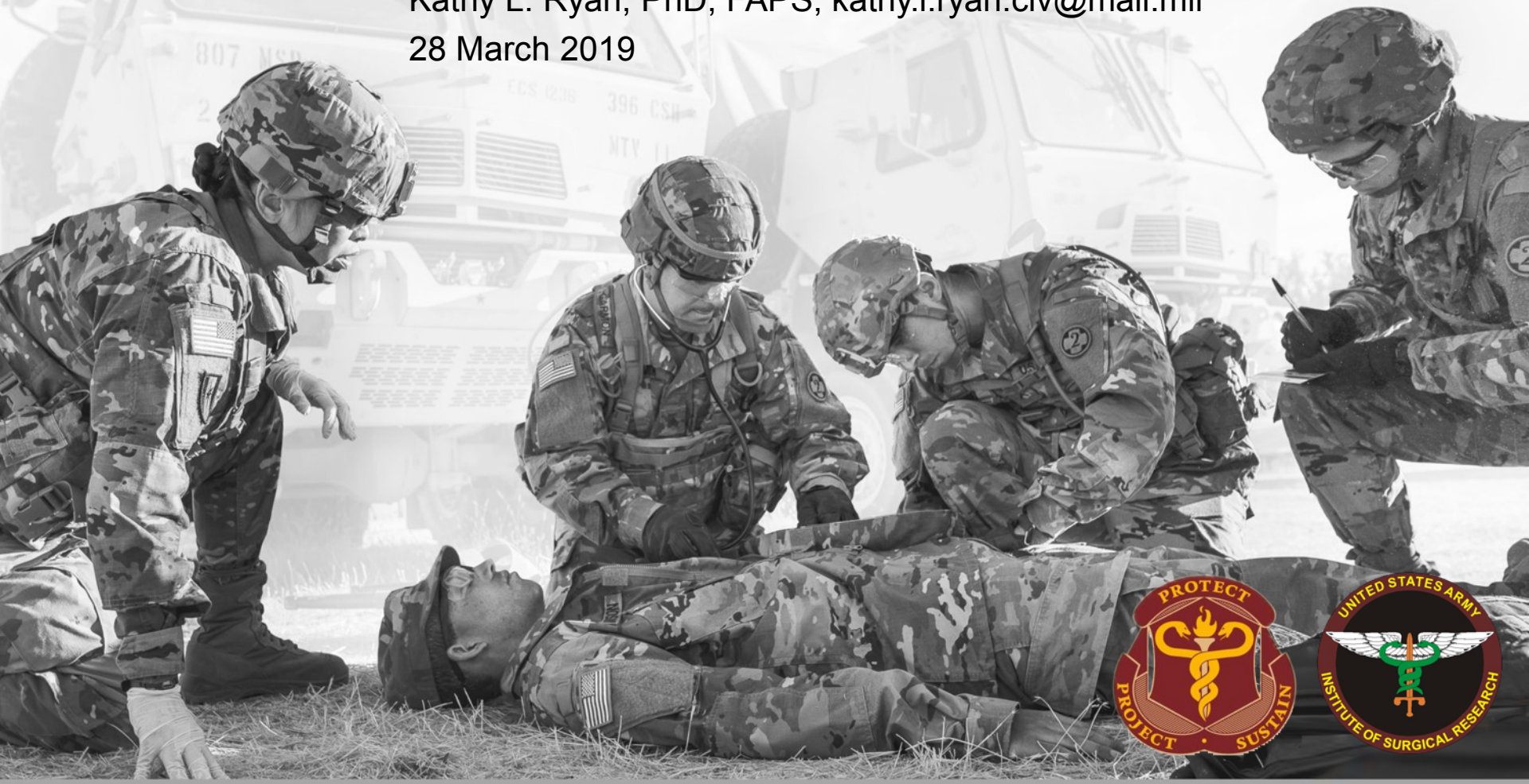
TXA

FDP

Tactical and En Route Care Research

Kathy L. Ryan, PhD, FAPS, kathy.l.ryan.civ@mail.mil

28 March 2019



Disclaimer

The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Mission and Goals

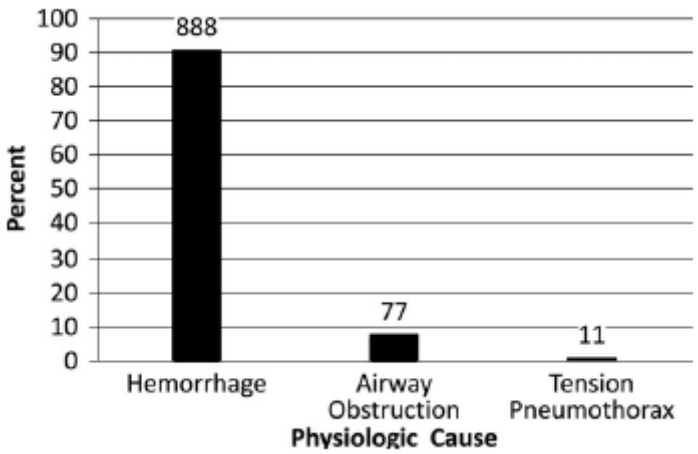
Mission: To conduct integrative and translational research focused on the prehospital environment (i.e., pre-surgery capability)

- » Care at level of combat medic or battalion aid station
  - » Corrective care: Immediate stabilization of casualties
  - » Protective care: Prevent known sequelae to traumatic injury

Active Research Areas

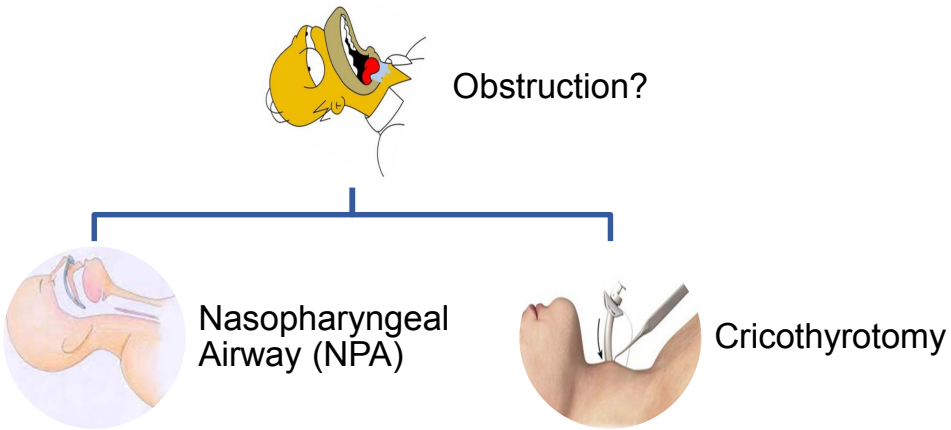
- Airway management
- Battlefield pain management
- Acute kidney injury (AKI) during prolonged care
- Blast injury and hemorrhagic shock
- Remote Trauma Outcomes Research Network (RemTORN)

Airway Management



2nd leading cause of potentially survivable death on the battlefield

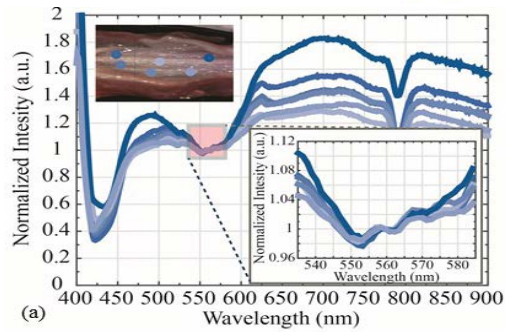
(Eastridge et al., J Trauma Acute Care Surg, 2012)

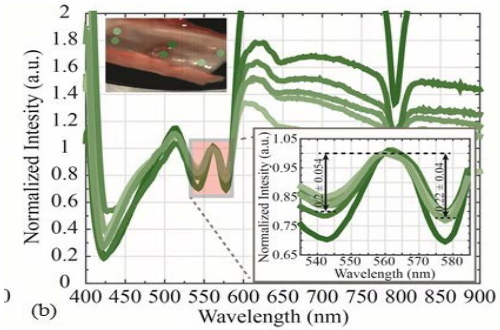


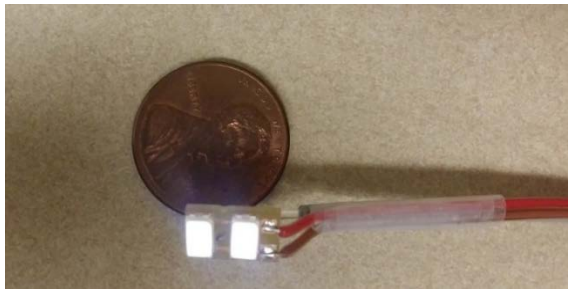
- Medics have 10-35% failure and 20% complication rates of endotracheal intubation *(Adams, J Trauma 2008; Mabry et al., PEC 2010)*
- Success of ETI drops to 50% without continuous practice *(Calkins and Robinson, J Trauma 1999)*
- 33% cric failure rate by medics *(Mabry, JSOM 2012)*
- Failure to achieve airway accounts for highest percentage of missed LSIs on battlefield *(Lairet et al, J Trauma 2012)*

Airway Management

- Can we make endotracheal intubation easier and/or more failproof?
  - Provide continuous feedback during procedure
    - Developed novel sensors to detect trachea vs esophagus
    - MRMC Tech Transfer Office seeking licensing partners
  - Semi-autonomous endotracheal intubation
    - Industry partner developing “blind” intubation (SBIR Phase II)
  - Re-engineer endotracheal tube
    - UTSA and UT-Health San Antonio
  - Digital extenders with haptic feedback for manual intubation
    - UTSA and UT-Health San Antonio



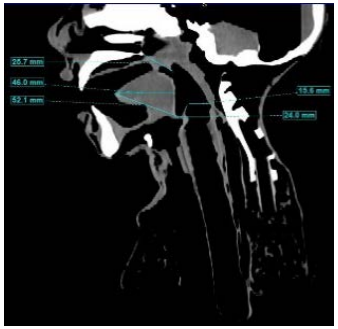


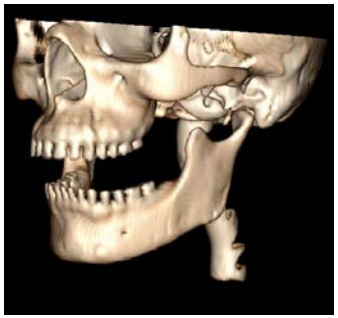


Nawn et al., J Biomed Optics 2016; Nawn et al., Anaesthesia 2019; Blackburn et al., submitted

Airway Management

- How anatomically correct are training manikins?
  - Importance: Used for training and medical device development
  - Physical and CT measurements
  - SynDaver, Laerdal, SimAir
  - Answer: Not anatomically correct when compared to
    - Values from scientific literature
    - CT scans from trauma patients (U of Michigan)
- Future SBIR topic to develop better manikin





Battlefield Pain Management

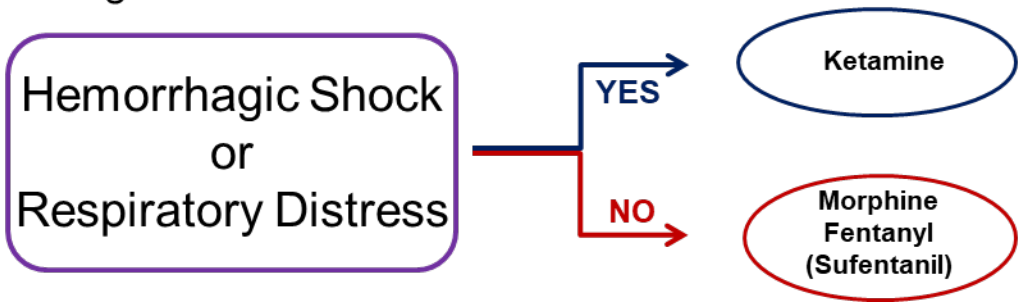
Committee on Tactical Combat Casualty Care (CoTCCC) Guidelines for Battlefield Pain Management

Butler, FK et al. A triple-options analgesia plan for tactical combat casualty care: TCCC Guidelines Change 13-04. J Special Operations Medicine 14:13-25, 2014

Selecting the Optimal Agent for Battlefield Analgesia

Primary goals of the triple-option approach to battlefield analgesia

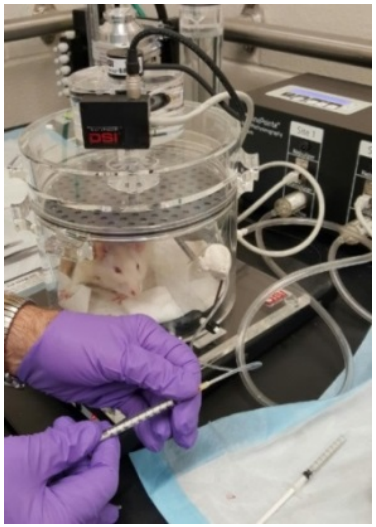
- To preserve the fighting force
- To achieve rapid and maximal relief of pain from combat wounds
- To minimize the likelihood of adverse effects on the casualty from the analgesic medication used

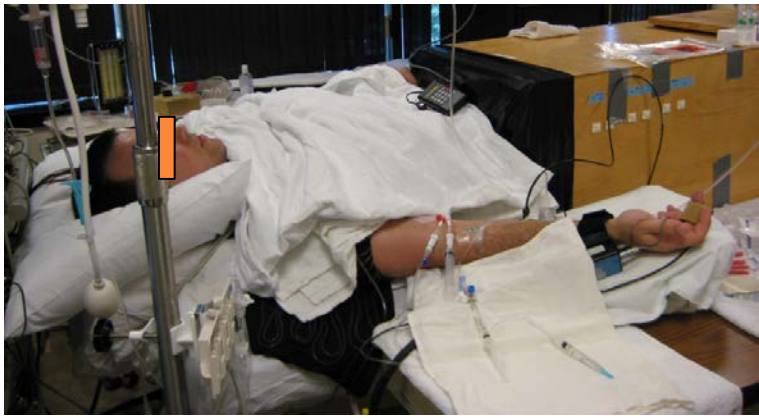


Although guidelines are based on provider recommendations, there are only a few (conflicting) laboratory studies that have assessed the impact of analgesics on the ability to tolerate and survive hemorrhage

Battlefield Pain Management

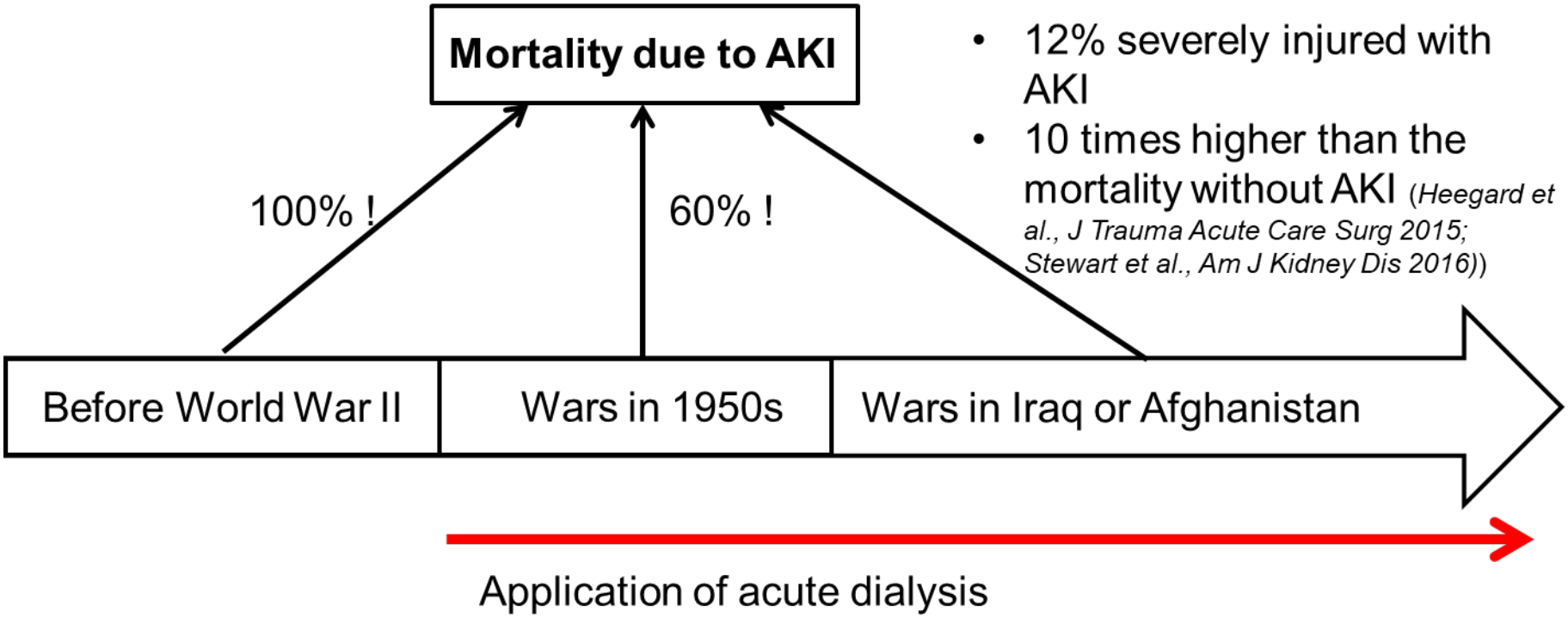
- Testing in conscious rat model of orthopedic trauma + hemorrhage
  - Ketamine has no adverse effects on cardiorespiratory function or ability to survive hemorrhage
  - Ongoing tests of morphine, fentanyl and sufentanil
  - Future: Tests of promising non-opioid analgesics in development
- Testing in healthy human volunteers in simulated hemorrhage – UT Southwestern Medical School
  - Ongoing tests of ketamine, morphine and fentanyl
  - Physiological mechanisms





Acute Kidney Injury during Prolonged Care

Combat-related acute kidney injury (AKI) predicts mortality



- 12% severely injured with AKI
- 10 times higher than the mortality without AKI (*Heegard et al., J Trauma Acute Care Surg 2015; Stewart et al., Am J Kidney Dis 2016*))

- Risk for AKI will increase during PFC
  - Full volume resuscitation may not be available (within 1 hr of injury)
  - Prolonged tourniquet use or crush injury → rhabdomyolysis

Acute Kidney Injury during Prolonged Care

- Establishing rat AKI models
  - Hemorrhage with and without resuscitation
    - What is ischemic “tolerance time” for kidney
  - Prolonged tourniquet use
    - Rhabdomyolysis
- Explore protective treatments that could be used at point of injury
  - Limb cooling (for tourniquet study)
  - Other drugs
    - Decrease metabolism?
    - Increase cellular energy?

Blast Injury and Hemorrhagic Shock

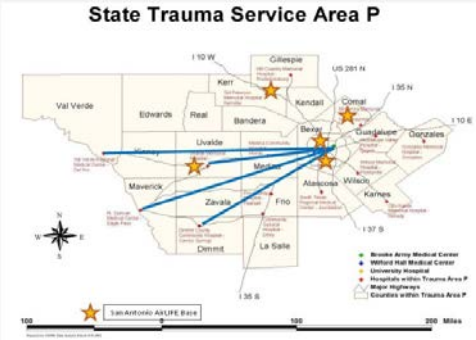
- Does blast injury/TBI affect the ability to survive hemorrhage? Does hemorrhage worsen TBI?
  - Combine blast injury with established rat models of hemorrhage
- Test platform for resuscitation strategies/drugs to protect brain without worsening hemorrhage physiology
- Engaged investigators at Walter Reed Army Institute of Research (WRAIR)
  - Neurotrauma
  - Blast injury

Remote Trauma Outcomes Research Network (RemTORN)

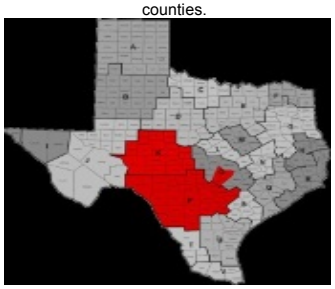
- » FY15-FY19 grant to Southwest Regional Advisory Council (STRAC); PI: COL (Ret) Brian Eastridge, MD (UT Health – San Antonio
- » Goals:
  - » To develop and implement a research platform for the study of traumatic injury occurring in rural settings
  - » Capture and study data from POI through Level 1 trauma center

- Example projects:
  - Damage control resuscitation
  - Medical Devices (CRI, ITD)
  - Patient motion during transport
  - Prehospital analgesia

STRAC
Southwest Texas Regional Advisory Council



Southwest Texas Regional Advisory Council (STRAC), Trauma Service Area P, encompasses over 26,000 square miles in southwest Texas and 22 counties.



Development Pipeline

Current Snapshot of Functional R&D Stages

Discovery-Knowledge
(6.1/6.2/6.3)
Topic Areas
TRL 1-3

Discovery-Product
(6.2/6.3)
Specific Candidate Concepts/Drugs/Devices
TRL 3-4

Late Discovery/Transition (6.3)
Pre-clinical & Early Clinical Studies
on Selected Lead Concept/Drug/Device Expected Transition w/in 2 yrs
TRL 4-5

Full (Clinical) Development
(6.4/6.5)
Specific Product
TRL 5-9

- Anatomical and physiological markers for airway Injury in large animals and PMHS
- Characterization of animal models of pain (Joint with new pain task area)
- Development of small animal model of AKI
- Development of small animal model of blast Injury and hemorrhage
- Determination of TBI effects on hemorrhage responses in small animals

- Semi-autonomous airway management device
- Feedback sensor to assist in intubation (component of airway management device)
- Assessment of drugs for pain management without cardiorespiratory effects

- TBD

- Compensatory Reserve Index (CRI)*

*Recent FDA approval

Knowledge Products To Support Clinical Practice

- Improved airway management techniques and procedures
- CPGs for Battlefield Pain Management
- CPG for Prolonged Field Care

Go/no go Decision Point

Challenges

- Point of injury care
  - Usable by combat medics
    - Need automated diagnostic capabilities to enhance clinical judgment
    - Need autonomous or semi-autonomous treatment for difficult procedures
  - Low power requirements
  - Low size/cube/weight
- Prolonged care requires more protective strategies
  - What can combat medic do to not only provide immediate stabilization but also protect against or delay pathophysiology?
- Requires innovative technology solutions
  - Biomedical engineering expertise
    - Industry via SBIR program or CRADA
      - Semi-autonomous endotracheal intubation (Phase II SBIR)
      - Autonomous pneumothorax detection and treatment (Phase I SBIR)
    - Academia
      - UTSA
      - UT Health – San Antonio
      - ???

Tactical and En Route Care

- Kathy L. Ryan, PhD
- Megan Blackburn, PhD
  - Corinne Nawn, PhD candidate
  - Cassandra Rodriguez, BS
- Carmen Hinojosa-Laborde, PhD
- Harold Klemcke, PhD
  - Mariam Calderon, BS, MS
  - Brian Connor, BS
  - Samantha Perez, BS
- Lusha Xiang, MD
  - Alfred Calderon, BS
- Luciana Torres, PhD
- CPT Ian Hudson, MPH, DO
- Gary Muniz (lab manager)

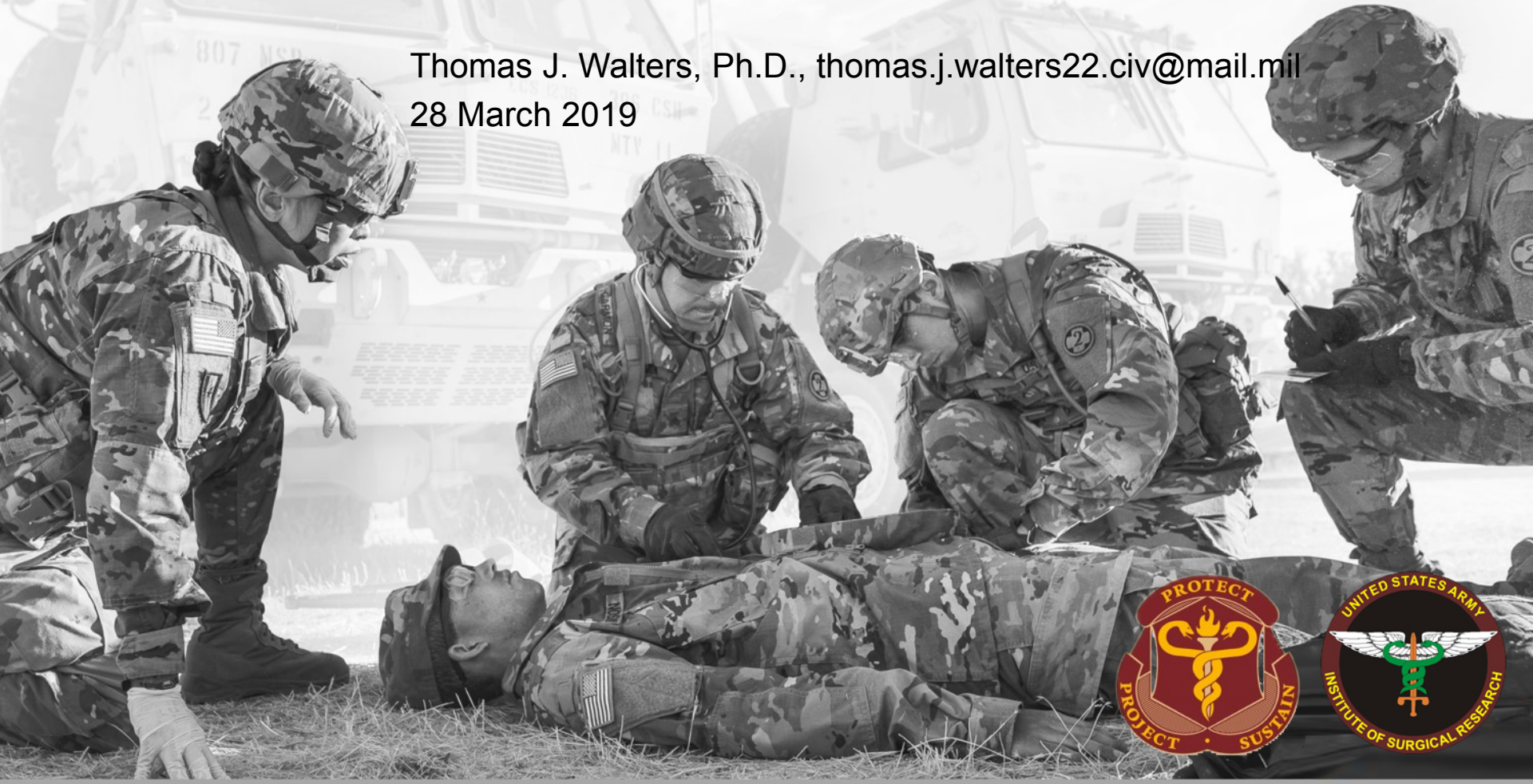
TEAM

Together everyone achieves more.

Expeditionary Critical Care Research

Thomas J. Walters, Ph.D., thomas.j.walters22.civ@mail.mil

28 March 2019



Disclaimer

The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

These studies were conducted under protocols reviewed and approved by the US Army Medical Research and Materiel Command Institutional Review Board and in accordance with the approved protocols.

Mission and Goals

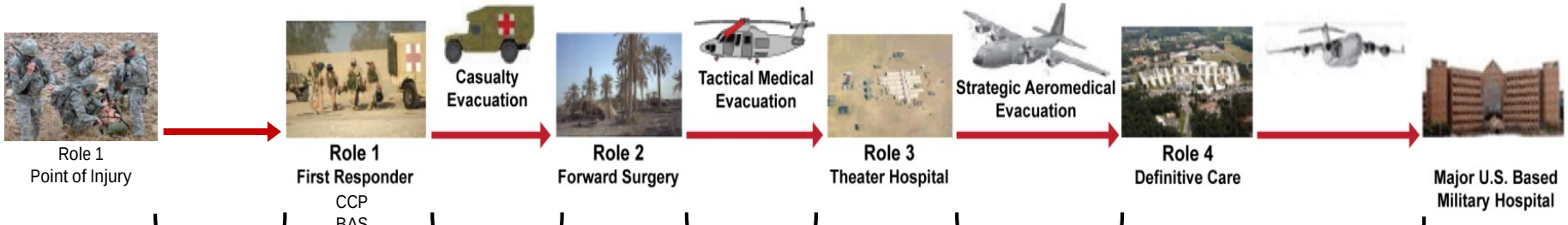
» **Mission:** To conduct integrative and translational research focused on the diagnosis, prevention, and treatment of ***secondary sequela*** that develop under ***delayed evacuation and prolonged care***

Goal: Push critical care medical capabilities **Far Forward** to provide organ support, decision support and treatment for first-responders and far-forward medical personnel

Roles of Care

Prolonged Care

Prolonged Field Care (PFC)



En Route Casualty Care (ERCC)

Battlefield Resuscitation & Immediate Stabilization Casualty Care (BRISCC):

Active Research Areas

- Mitigating Organ Injury
  - Extracorporeal Life Support (ECLS)
  - Immune modulation
  - Sepsis-detection/treatment
- Mitigating Ischemia/Reperfusion Injury
  - Resuscitative Balloon Occlusion of the Aorta (REBOA) for Non-Compressible Truncal Hemorrhage
  - Limb Salvage following Ischemia-vascular injury, crush injury
- Mitigating the Impact of Prolonged Immobilization
  - Pressure Ulcers

Mitigating Organ Injury

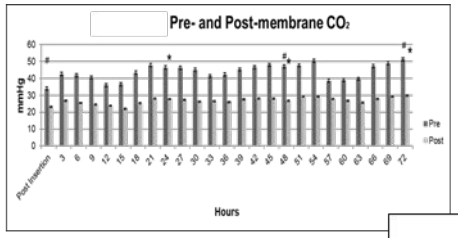
- Background (OEF/OIF):
  - Blast-induced injuries 70-80% of casualties
  - Blast lung injury – 6-11% of casualties
  - Burns – 34% ARDS
  - AKI-12% of casualties

- Gap: Army units are not capable of managing organ dysfunction secondary to trauma at point of need (POI - ROC3), when evacuation may be delayed or is unavailable; Field deployable toolset to prevent major organ injury/failure is needed.

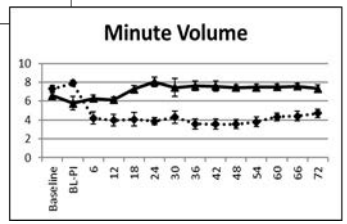
Mitigating Organ Failure- Extracorporeal Life Support (ECLS)

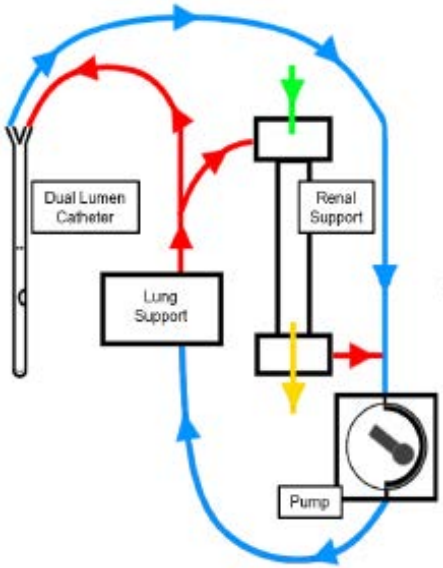
- Heparin-free ECLS
- CRRT-burn, shock, AKI
- Mini-ECLS for renal support
- Extracorporeal Carbon Dioxide Removal (ECCO2R) for ventilation

Headed by Dr. Andriy Batchinsky



$ECCO_2R$ leads to reduction in MV burden, enabling lung protection

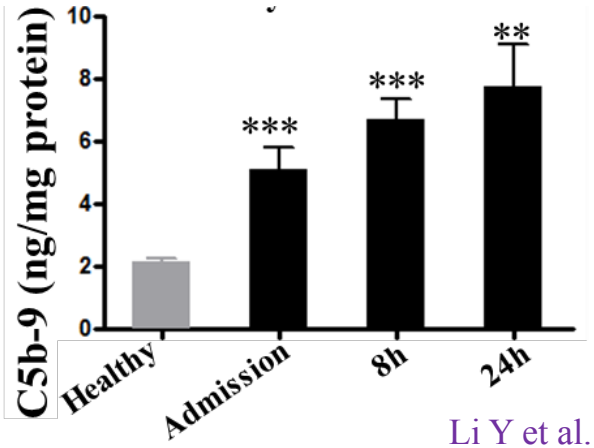


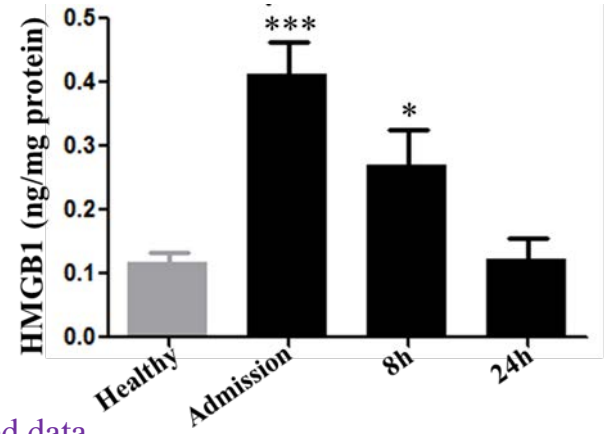


Thomas J. Walters, PhD; thomas.j.walters22.civ@mail.mil

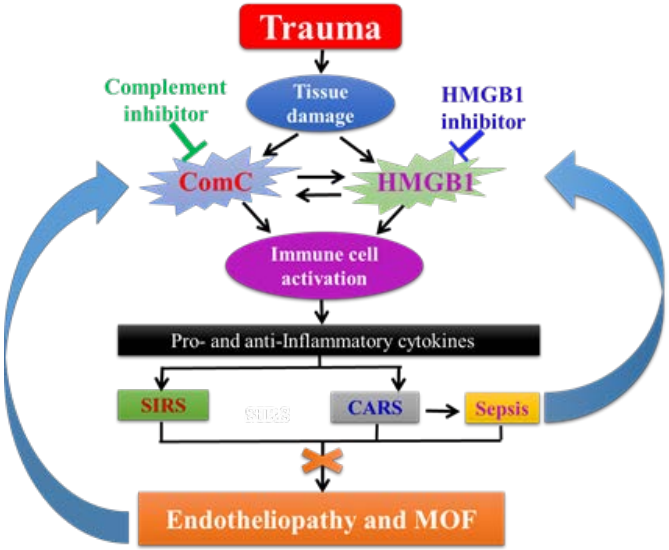
Mitigating Organ Injury-Clinical Observation

Early complement activation and systemic release of HMGB1 in military trauma patients



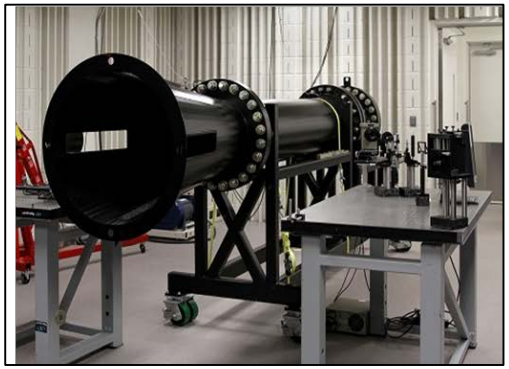


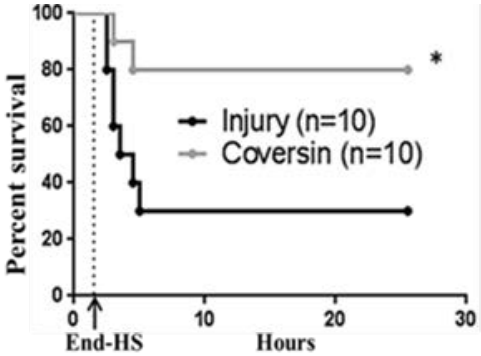
Li Y et al. Unpublished data

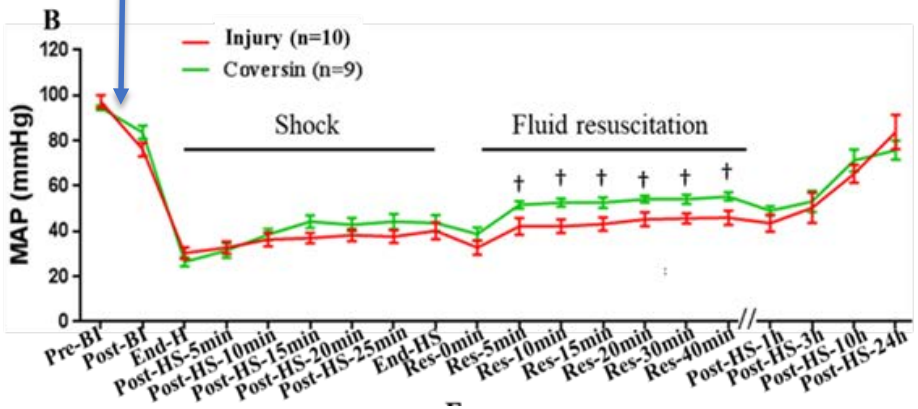


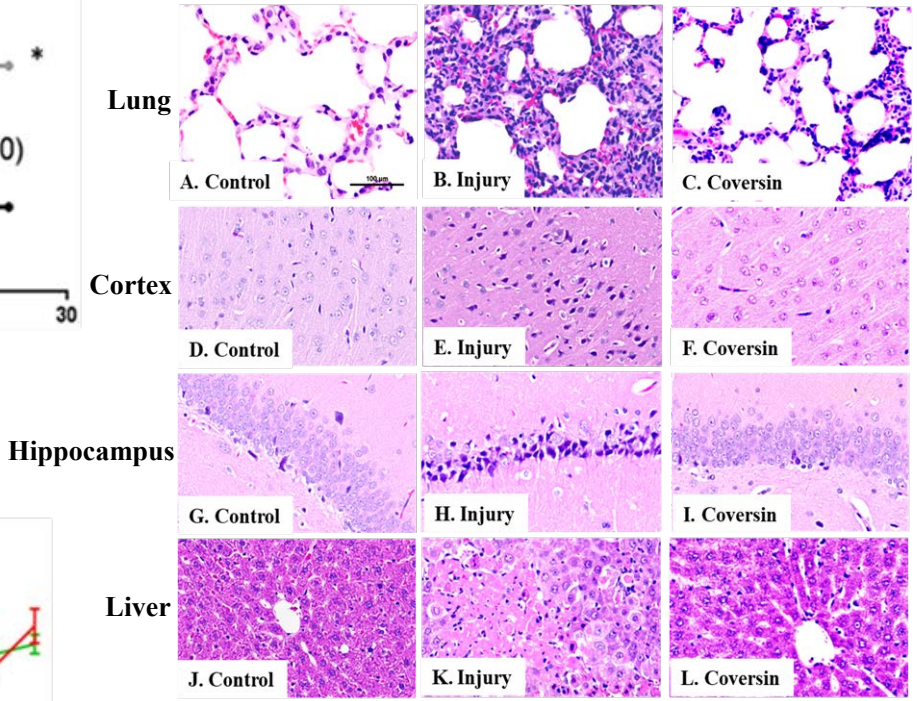
Mitigating Organ Injury: Pre-Clinical Study

C5 inhibitor treatment increases survival and mitigates organ damage in a rat blast and hemorrhage model





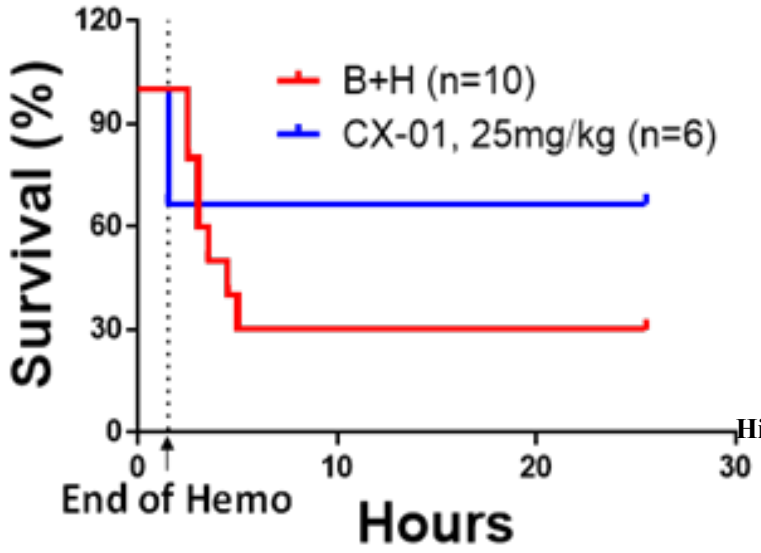


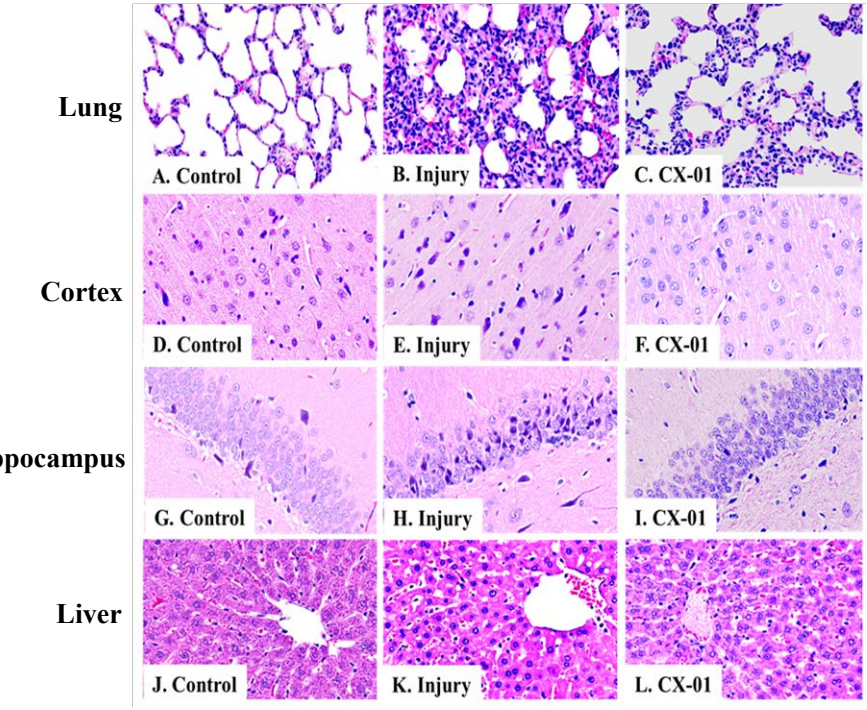


Li Y et al. Unpublished data

Mitigating Organ Failure: Preclinical Study

HMGB1 inhibitor increases survival and mitigates organ damage in a rat blast and hemorrhage model

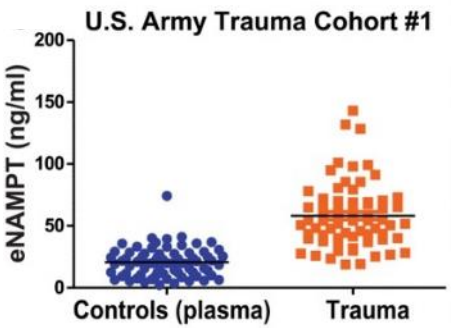




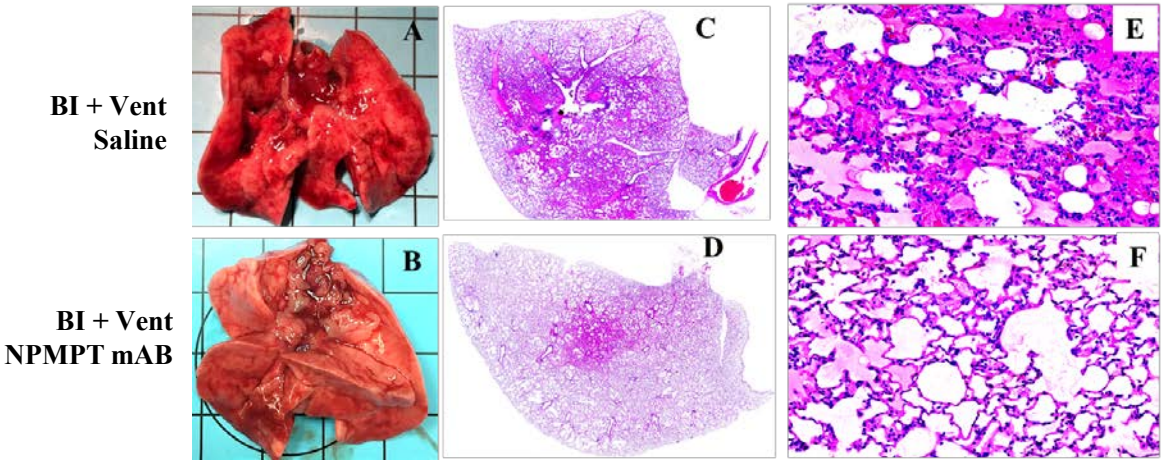
Li Y et al. Unpublished data

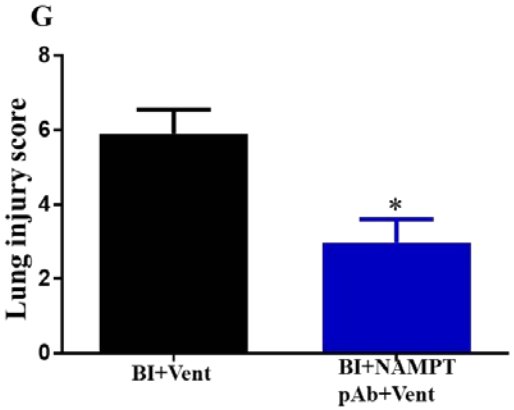
Mitigating Organ Failure: Preclinical Study

Increased levels of adipocytokinese NAMPT in ARDS patients and trauma patients



NAMPT pAb ameliorates blast/ventilation-induced acute lung injury in rats

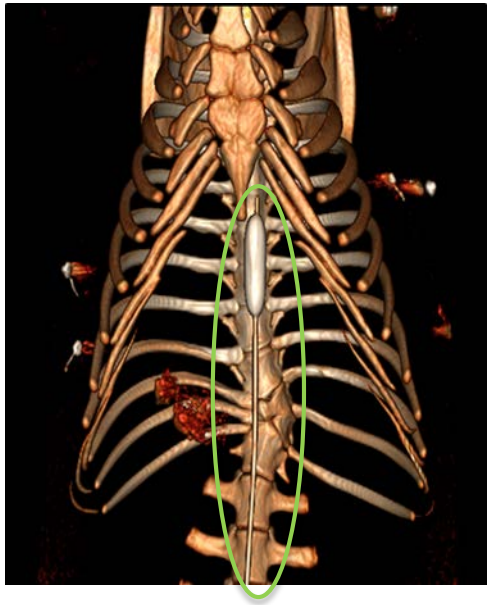


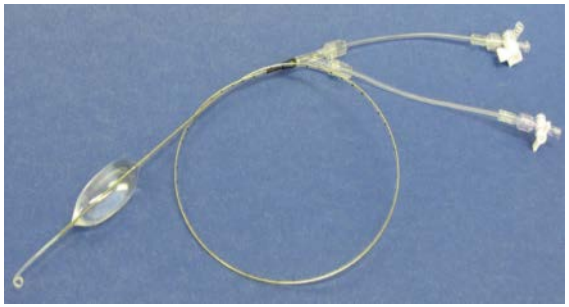


Li Y et al. Unpublished data

Mitigating Ischemia/Reperfusion Injury

- Noncompressible torso hemorrhage (NCTH) is the last remaining major cause of preventable death on the battlefield
- *REBOA offers method to temporize hemorrhage in Torso
- Profound distal ischemia = 40 minute limit
- Method(s) to increase ischemic time needed



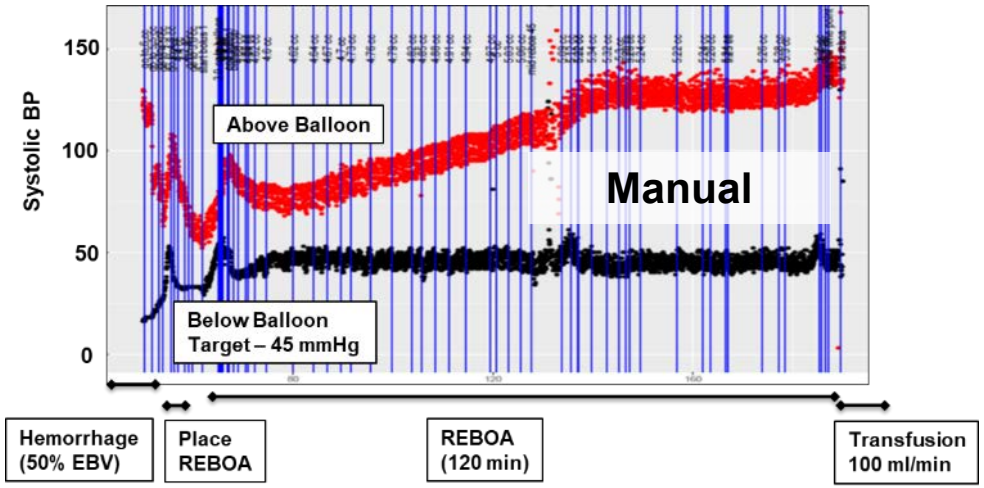


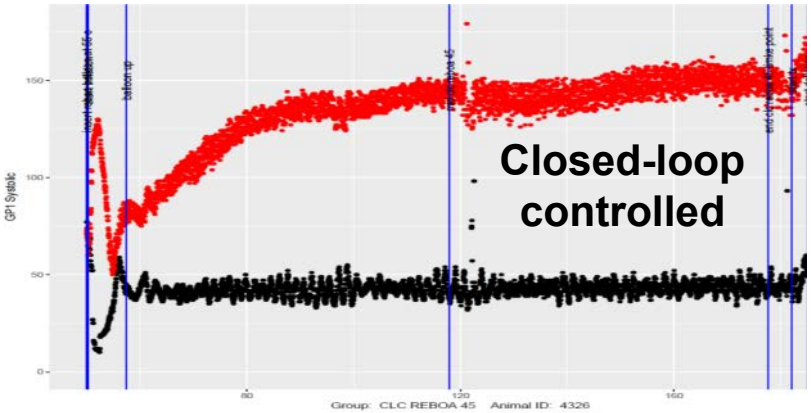
*Resuscitative Endovascular Balloon Occlusion of the Aorta

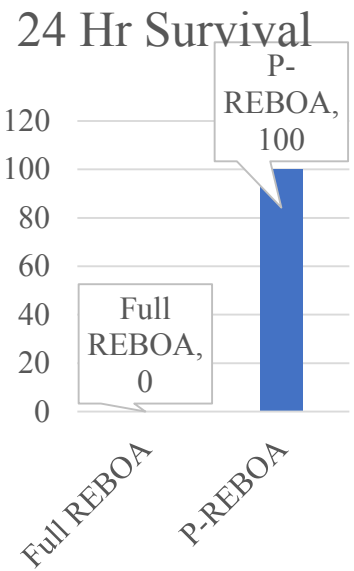
Thomas J. Walters, PhD; thomas.j.walters22.civ@mail.mil

Permissive-Hypotension REBOA (P-REBOA) Improves Survival

Porcine Model of Exsanguination



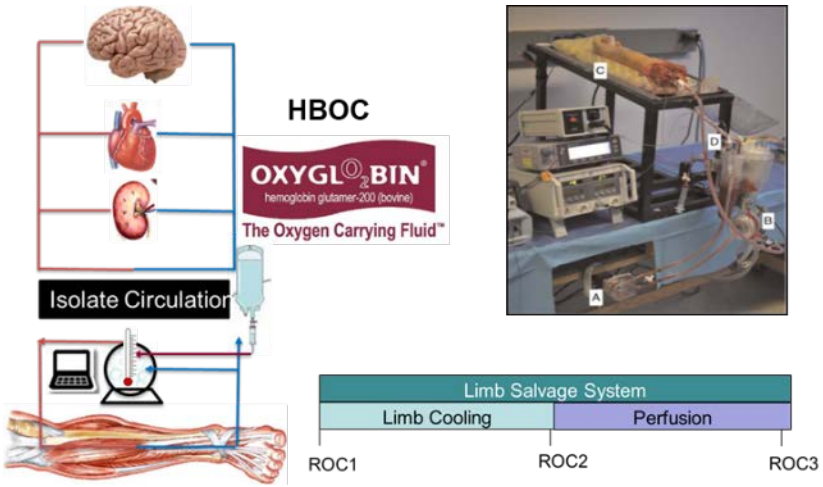




Mitigating Ischemia/Reperfusion Injury

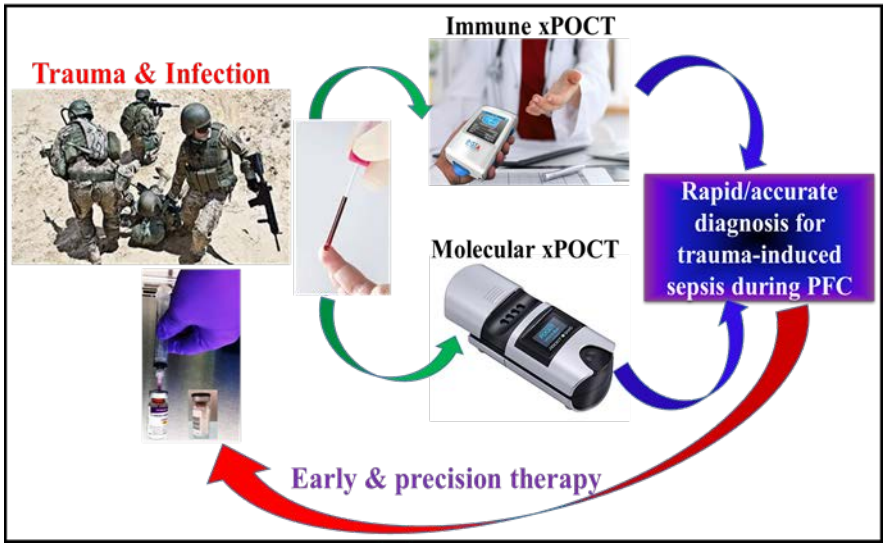
- Widespread use of tourniquets in OEF/OIF significantly increased survival from extremity hemorrhage
- Median tourniquet time – 60 min.
- No limb loss due to tourniquet use
- During PC longer tourniquet times
- Need methods to preserve limbs during occlusive vascular treatments (e.g. tourniquet)

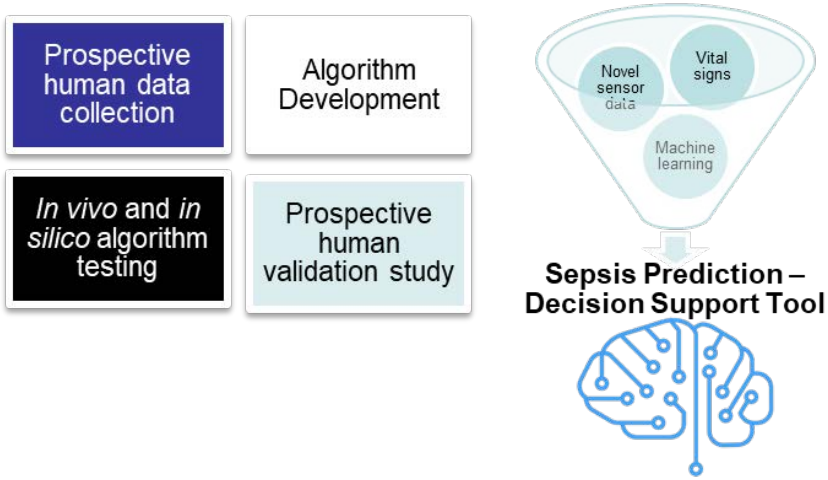
Limb preservation system



Battlefield Sepsis: Mitigation and Detection

- Decision support
  - machine learning algorithm (sepsis and organ failure)
  - Point of care-biomarker based
- Novel treatments-immune modulation





Thomas J. Walters, PhD; thomas.j.walters22.civ@mail.mil

Expeditionary Critical Care

Development Pipeline – Current Snapshot of Functional R&D Stages

Discovery-Knowledge (6.1/6.2/6.3)
Topic Areas
TRL 1-3

- Characterize material effects on coagulation for ECLS
- Investigate cell free-MSC based treatments to prevent organ damage
- (Patho)Physiological responses and resuscitation using partial/next generation Endovascular Balloon Occlusion of the Aorta (REBOA) catheters (Joint with DCR)
- Develop small and large animal models of machine perfusion of vascularly isolated limbs

Discovery-Product (6.2/6.3)
Specific Candidate Concepts/Drugs/Devices
TRL 3-4

- ECLS+ REBOA for resuscitation
- Miniaturized, wearable ECLS
- Perfusion strategies for REBOA using closed-loop system
- Immunomodulation for trauma and hemorrhagic response (screening complement inhibitors)
- Test selected HBOCs and oxygen carrying solutions on the physiology of "ischemic" muscle during and after isolated limb perfusion

Late Discovery/Transition (6.3)
Pre-clinical & Early Clinical Studies
on Selected Lead Concept/Drug/Device Expected Transition w/in 2 yrs
TRL 4-5

- Integrated ECLS for lung and kidney support
- Partial REBOA using closed-loop system
- Develop Limb Cooling System to Preserve Ischemic Extremity for Prolonged Field Care (DHP-SBIR)
- Pressure ulcer reducing litter pad (DHP-SBIR)

Full (Clinical) Development (6.4/6.5)
Specific Product
TRL 5-9

- REBOA Catheter (Joint with DCR) *

***Recent FDA approval**

Go/no go decision gate

Knowledge Products That Support Clinical Practice/Operations

- Treatment Guidelines for ECLS Use in Far Forward Environment (during ground evac)
- New Generation Endovascular Balloon (REBOA)
- CPG on adjunct use of ECLS and MV in trauma and for prolonged field care
- CPG for use of REBOA in pre-hospital setting
- Wearable ECLS
- Complement measurement and treatment monitoring guidance

anthony.e.pusateri.civ@mail.mil

Unclassified

Challenges

- Inability to evacuate casualties will result in increase in secondary injuries and complications occurring at POI and lower/less capable ROC
- Managing these casualties will be done by providers with minimal or no medical training-lack skill to prevent, predict, diagnose, and treat complications
- Goals:
  - Return of Soldiers to operational readiness
  - Sustain casualty until evacuation to higher level of care

- Technological solutions are required that are capable of:
  - Decision support-enhance clinical judgement/cognitive offloading
  - Diagnostic capabilities-linked to decision support
  - Autonomous/closed loop systems
    - Management of organ dysfunction
    - Resuscitation requirements
    - Limb perfusion
    - Infection/Sepsis
    - Nursing care
- Technologies must be:
  - Rugged
  - Small **s**ize, **w**eight, **a**nd **p**ower (SWAP) requirements
  - Easy to use

Strategies to Meet Challenges

- Leverage capabilities of industry and academia
  - Industry via SBIR program or CRADA
    - Limb Cooling Device (Phase I SBIR)
    - Pressure Relieving Transport Pad (Phase I SBIR)
  - Academia
    - UTSA
    - UT Health – San Antonio
    - Univ. of Arizona
    - University of Virginia
    - Univ. Harvard, Medical School
    - University of Michigan-Ann Arbor
    - Southern Alabama University
    - UCSD
  - Industry
    - Vascular Perfusions (San Antonio, TX)
    - Prytime Medical Devices, Inc. (Bourne, TX)
    - Aqualung Therapeutics
    - Akari Pharmaceuticals, London
    - Pharming Group NV (Netherlands)
    - Aurin Biotech Inc. (Vancouver, Canada)
    - Cantex Pharmaceuticals (FL)
    - Alexion Pharmaceuticals, Inc (New Haven, CT)
    - Instadiagnostics Inc. (Philadelphia, PA)

The Team

Research Staff

- Thomas J. Walters, PhD
- MAJ Danial Erwin, PhD
- COL(Ret) Leopoldo Cancio, MD
- Corina Necsoiu, MD
- Yansong Li, MD
- Benjamin Antebi, PhD
- Zhangsheng Yang, MD
- Arezoo Mohammadipoor, DVM, PhD
- Bryan Jordan, RN

Visiting Fellows

- Seok-Jae Lee, MD

Support Staff

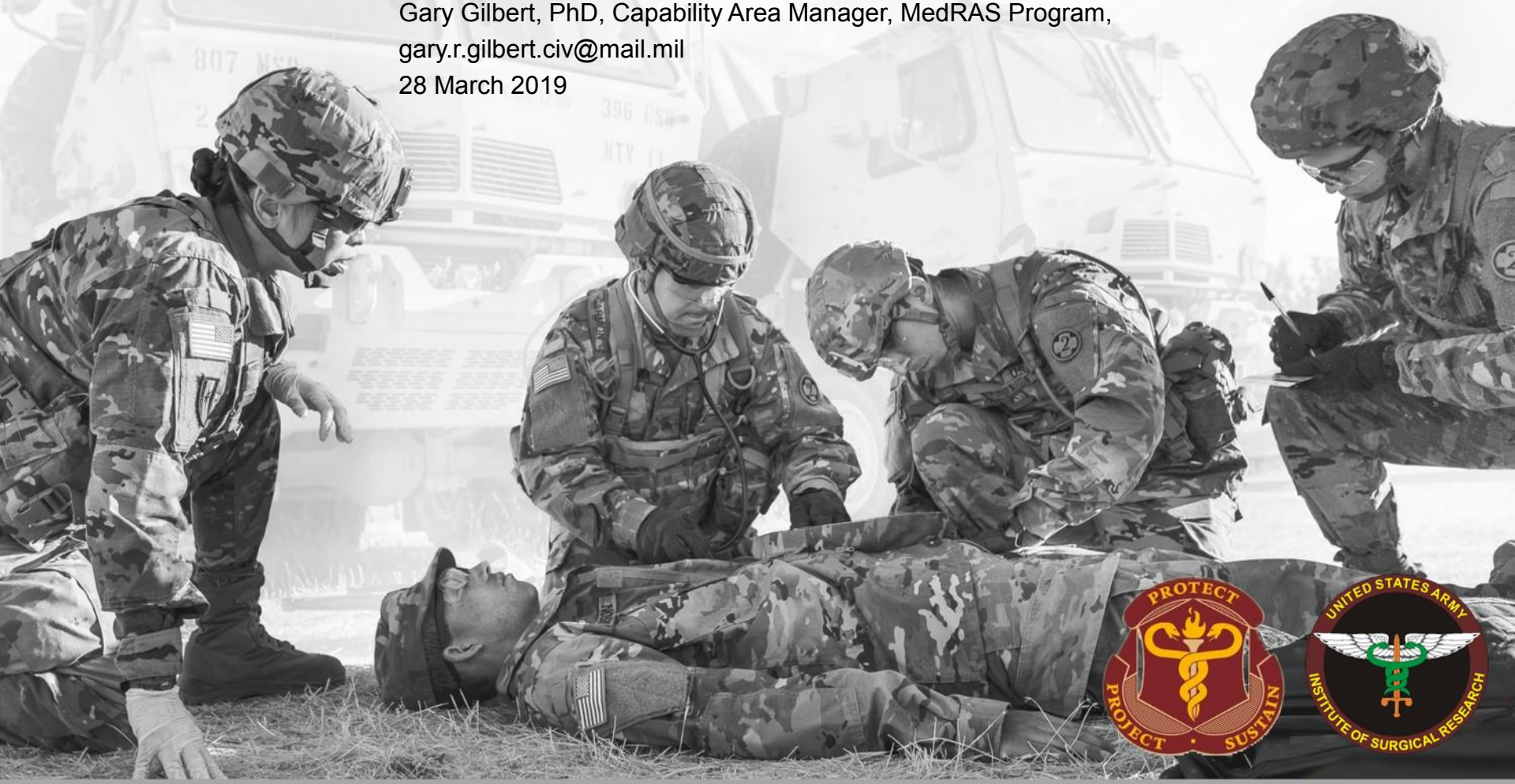
- Michael Lucas
- Celina Valdez
- Rodolfo (Jun) De Guzman
- Julie Hampton
- Brendan Beely
- Lucero Alvarado
- Luis Rodriguez
- SPC Stacey Bernetskie
- SPC Pedro Garcia

Students/Post Docs

- Lucero Alvarado
- Teryn Roberts

Clinical Decision Support and Automation Research

Jose Salinas, PhD, Branch Chief, jose.salinas4.civ@mail.mil
Gary Gilbert, PhD, Capability Area Manager, MedRAS Program, gary.r.gilbert.civ@mail.mil
28 March 2019



Disclaimer

The opinions or assertions contained herein are the private views of the author and not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Conflicts of Interest: None

Multi-Domain Battle Concepts
Constraints on Medical Resources

Limited freedom of movement for conventional vehicle platforms (both air and ground) to provide emergency medical resupply and casualty evacuation

- Wide Dispersion of Maneuver Units
- Area denial (e.g. CBNRE)
- Air Superiority not assured.
- 6-Dimensional threats (air, land, subterranean, maritime, space, and cyber).

Limited Medical Resources

- High risk Environments for manned assets
- Delayed Evacuation / Prolonged Field Care
- Risk of loss of irreplaceable human resources.

Robotics & UMS as Force Multipliers

- When conventional manned assets are denied access
- When air superiority is not assumed
- When medical resources are severely constrained
- As UMS replace manned “vehicles of opportunity”

Advantages:

- Performance – Speed, Maneuverability, Endurance
- Smaller Landing Zones (LZs)
- Cost & Capacity***

Supporting MOD

Better Training

New/Improved Technology Solutions

More POI Providers

- ✓ Improved Devices
- ✓ Decision Support
- ✓ Monitoring
- ✓ Automation

Two Programmatic Support Functions

New DoD Programs To Support MOD

- Joint with Telemedicine and Advanced Technology Research Center (TATRC)
- Virtual Health
- Autonomous and Unmanned Medical Systems
- Medical Robotics

New USAISR Engineering/IT Capability Support Functions

- Engineering and Software Development for Combat Casualty Care
- Simulation and Modeling
- Artificial Intelligence/Machine Learning/Deep Learning
- Decision Support/Automation for Critical Care

Medical Research Capabilities

- New Sensors
- New Diagnostic Indices
- Modeling & Simulation
- Machine Learning
- Data Fusion
- Digital Data Processing

- Automated Diagnostics
- Patient Management Algorithms
- New Display Modalities
- Hybrid Automation of CC processes
- Prediction Systems

- Open/Closed Loop Systems
- Hybrid Control Systems
- Control Algorithms

Smart Monitoring

Decision Support

Automation

Support for Levels of Research Automation

RISK

COMPLEXITY

- Advanced Graphical User Interfaces (GUIs)
- New Sensor Modalities
- Data Fusion Algorithms (new Indices)
- Decision Support and Diagnosis
- Open-Loop Control and Automation
- Hybrid Closed-Loop Control and Automation
- Full Closed-Loop Critical Care Patient Management and Control

Medical Simulation & Information Sciences
New Army Science &Technology Task Areas

To support medical care delivery in dispersed and complex environments through futuristic technologies.

AUTONOMOUS AND UNMANNED MEDICAL CAPABILITY

VIRTUAL HEALTH

Threats

Dispersed Operations

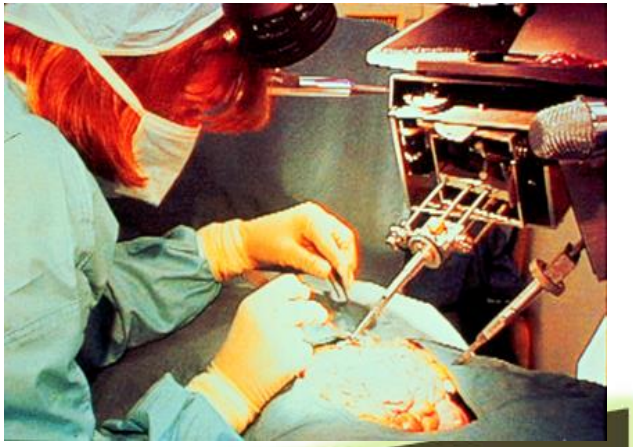
Contested Air Space

Limited Casualty Evacuation

Delayed Definitive Patient Care

Lo/No Comm Environments

MEDICAL ASPECTS OF MAN-MACHINE TEAMING: MEDICAL ROBOTICS



Multi-Year P6.2 & 6.3 Army S&T POM: 2018 -2024

Secretary of the Army Priorities - Lethality

- Army Secretary Mark Esper: "As I return to duty, I want you to know that my ***first priority is readiness***…. with an immediate focus on preparing for a high-end fight against a near-peer adversary"
  - ✓ Modernization and reform rounded out his top three, which go hand in hand with the
  - ✓ Focus is on six areas crucial to combat; Long-Range Precision Fires, the next-generation combat vehicle, Future Vertical Lift, the network, air and missile defense, and ***soldier lethality*** *

    (from "**New in 2018: Army secretary lays out his priorities", Army Times 27 Dec 2017)**

- LTG Edward Cardon* visit to MRMC 17 Apr 2018***: "How does this contribute to Lethality?"***

  * charged with standing up new Army Modernization Command

"The more things change……." → **TWO Primary Weapons Systems off Line!!**

Medical Robotic & Autonomous Systems (RAS)
- Gaps Assessment -

Required Capabilities *	
1. Army Units lack fully adequate **medical evacuation capability and capacity in select environmental and operational conditions** due to shortfalls in platform availability, mobility, protection, all-weather/visibility, and responsiveness across the operational area. *Relevant Extremely/High Risk CNA Gaps:* *501244, 461752, 203567, 550200, 202506*	2. Army Units with medical capability (point of injury and Role 1/2) possess **limited capability to provide prolonged field care and enroute care** (resuscitative and stabilizing medical or surgical treatment). *Relevant Extremely/High Risk CNA Gaps:* *501244, 501281, 461752, 203225, 203554, 502277*
Potential RAS Solutions *	

• **RAS Patient Extraction & Evacuation in Complex Environments**
  • Cargo/utility RAS transport pressed into service in CASEVAC, additive to manned MEDEVAC force structure to add capacity
  • RAS CASEVAC for reduced risk operations in CBRN and DVE
  • RAS Wing-men (escort, scout) to support MEDEVAC
  • RAS delivery of CLVIII and blood products
	• **Robotic & Autonomous Critical Care System**
	  • Enroute care during prolonged field care & RAS evacuation
	  • Closed-loop respiratory, fluid, pharmacology management
	• **Tele-surgical Robotic Operative Network**
	  • Telerobotic & semi-autonomous surgery
	• **Robotic Assistant For Medical Treatment Facilities**
	  • Patient monitoring & mentoring (cognitive offload)

Collaborative Partnerships (Past, Present & Future)	
• Office Naval Research – Autonomous Aerial Cargo Utility System • DARPA/OUSD(AT&L) / NAVAIR • ARL/AMRDEC/TARDEC/MCWL • USAARL, USAISR, USAMMDA, USAMMA PM MEDEVAC Mission Equipment	• ONR 34 (Autonomous Casualty Care System) • USAISR, USAMMDA, USAARL • Academia (Univ of Pittsburgh, Carnegie Mellon Univ, Stanford) • Small Business Innovation Research Program • DARPA, ARL, CERDEC, AFRL/MCWL, USSOCOM

*From Army Medical Command HRCoE CDID Medical Evacuation Proponency (MEPD) RAS Gaps Assessment and/or from ARCIC Unified Quest 18 RAS Workshop

Medical RAS Priorities

- Increase the survival rates of combat casualties & improve management of patients during PFC & reduce complications from injury
- Provide ground/air CASEVAC/MEDEVAC when manned systems not available or denied entry
- Increase capability and capacity for medical evacuation in select environmental and operational conditions
- Provide assessment, monitoring and enroute care during CASEVAC/MEDEVAC in UMS platforms
- Increase capability to provide prolonged field care and enroute care (resuscitative and stabilizing medical or surgical treatment).
- Increase capability to provide emergency battlefield resupply of critical medical Class VIII materiel.
- Extend medical & surgical expertise far forward
- Provide casualty extraction from hostile and complex environments
- Provide for patient safe-ride in UMS platforms
- Provide for RAS man-machine interaction & patient safety

Virtual Health Priorities

- Delivery of Critical Care in prolonged care (PC) and extended en route care
- Telemedicine value from limited bandwidth
- Medical decision support tools in no/low communication
- Tracking of patient care in Role 1 / 2
- Trauma and Tactical Combat Casualty Care (TCCC) support for isolated medics
- Medical technology to support unstable trauma patients during prolonged care
- Technologies to improve capabilities of low level providers at point of injury

ARCIC/RDECOM Initiative

- **ARCIC/RDECOM "Unified Quest 2018" Robotic Autonomous Systems (RAS)Applications Workshops**
  - 11-15 Dec 2017, Carlisle Barrack, PA (Echelons Above Brigade & Brigade & Below)
  - 5-9 March 2018, Fort Eustis, VA (Brigade Combat Team)
  - OBJECTIVE: Operationalizing the Future or RAS in Support of Multi Domain Battle

System #	Organization	System Name
1	Armored BCT Infantry BCT	Man Transportable Robotic System (Increment II)
2	Armored BCT Infantry BCT R&S BCT	Soldier Autonomous Sensor
3	Engineer BDE Maneuver Enhancement BDE Armored BCT	Husky Mounted Detection System
4	Engineer BDE Maneuver Enhancement BDE Armored BCT	Route Clearance Interrogation System
5	Armored BCT SBCT Engineer BDE Maneuver Enhancement BDE	Robotic Breach Vehicle
6	Engineer BDE Maneuver Enhancement BDE CBRN BDE Armored BCT Infantry BCT	Common Robotic System – Individual (CRS (I))
7	Engineer BDE Maneuver Enhancement BDE MP Brigade CBRN BDE Armored BCT Infantry BCT	Common Robotic System – Heavy (CRS (H))
8	Armored BCT Infantry BCT	Squad Multi-purpose Equipment Transport (SMET)
9	Armored BCT Infantry BCT R&S BCT	Joint Tactical Autonomous Aircraft Resupply System (JTAARS)
10	Armored BCT Infantry BCT SBCT R&S BCT	Micro UGV / Ultralight Reconnaissance Robot

System #	Organization	System Name
11	Armored BCT Infantry BCT	Soldier-borne Sensor (SBS)
12	Armored BCT Infantry BCT	Automated Convoy Operations (ACO)
13	Armored BCT	Tethered Unmanned Aerial System (TUAS
14	Armored BCT SBCT	Robotic Combat Vehicle - Direct Fire
15	Armored BCT SBCT	Robotic Combat Vehicle - Indirect Fire
16	Armored BCT Stryker BCT Infantry BCT R&S BCT	Robotic Combat (SMortarNet)
17	Armored BCT Stryker BCT Infantry BCT R&S BCT	Robotic Combat
18	ABCT, SBCT, IBCT, R&S BCT	RCV-Indirect/Fi Direct Engagem
19	MED BDE (SPT) (Medical Company, Area Support); also, applies directly to organic medical units at Echelons below brigade)	Robotic Patient Environm
20	MED BDE (SPT) (also applies to organic medical units at echelons below brigade)	Robotic Autonor Systems

System #	Organization	System Name
21	Armored BCT Infantry BCT SBCT R&S BCT	Screening Obscuration Module - Remotely Operated Signature Management System-Obscuration (SOM-ROSMS-O)
22	Engineer BDE Maneuver Enhancement BDE Armored BCT Infantry BCT SBCT	RCV-Counter Explosive Hazard (Next Generation Explosive Breacher (NGEB) (i.e. Mine Clearing Line Charge Replacement)
23	Armored BCT Infantry BCT SBCT	Large Area Multi-Spectral Smoke System
24	Armored BCT Infantry BCT SBCT	Obscurant Deception Device

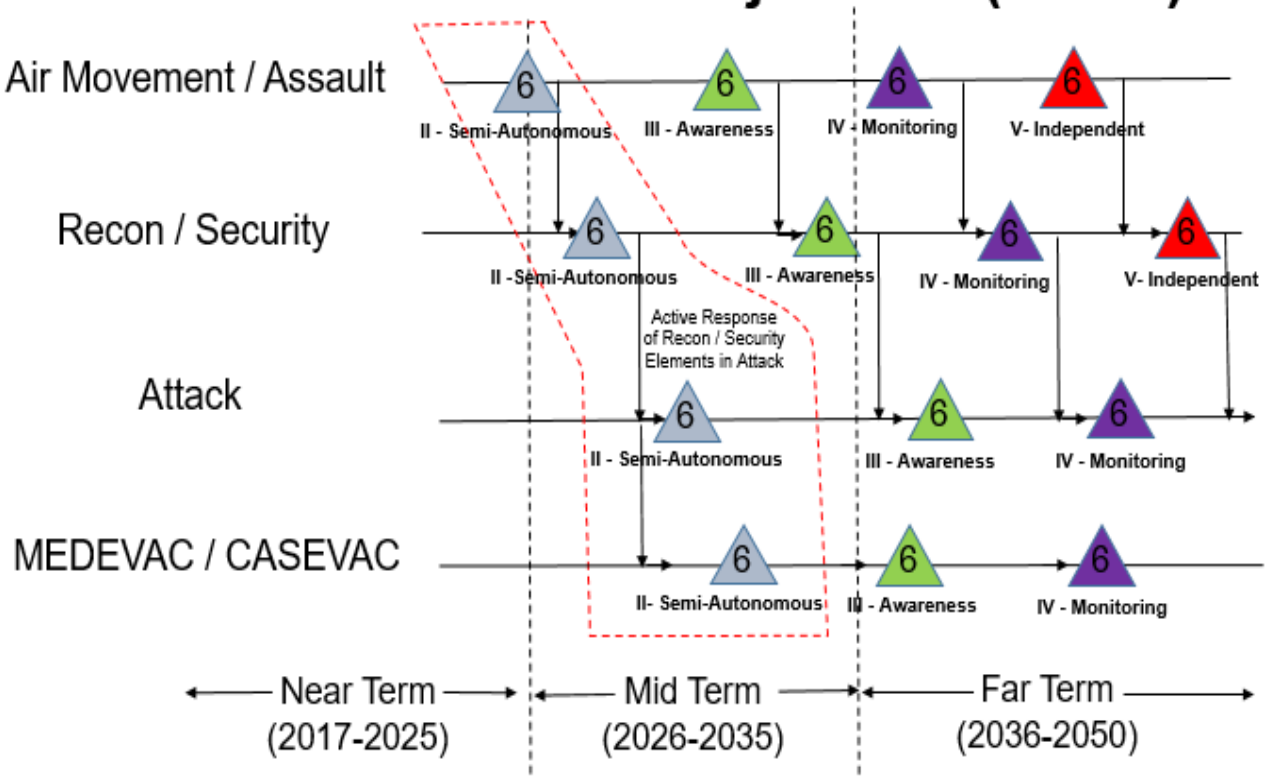
MED BDE (SPT) (Medical Company, Area Support); also, applies directly to organic medical units at Echelons below brigade) — Robotic Patient Extraction in Complex Environments

MED BDE (SPT) (also applies to organic medical units at echelons below brigade) — Robotic Autonomous Critical Care Systems

AMRDEC Initiative

- **AMRDEC Levels of Autonomy Working Group**
  - FY 2017-18. Report out 3rd Qtr FY18
  - OBJECTIVE: Development of Army Aviation RDT&E Roadmap

DRAFT Tech Demo Objectives (TRL 6)



Joint & NATO Initiatives

- **ASBREM Sponsored Joint "State of Science" Workshop in Autonomous Medical Evacuation (AME).**
  - Arlington, VA, 10-12 July 2018
  - OBJECTIVES:
    1. Provide visibility of medical needs to enable autonomous evacuation.
    2. Develop a common understanding of current capabilities and research objectives.
    3. Discuss the trajectory of enabling technologies and identify key technical challenges and gaps.
    4. Identify opportunities for coordination and novel partnerships across Communities of Interest (COI).
- **NATO Human Factors in Medicine Development of Autonomous Medical Systems for Tactical Evacuation. HFM-ET-167 Jan 2018-Jan 2019.**
  - USA leads with France, Great Britain, Canada
  - OBJECTIVES
    1. Establish common NATO concepts for leveraging emerging general purpose unmanned systems (UMS) platforms for medical missions.
    2. Establish a common NATO research and development roadmap for robotic, autonomous, and unmanned capabilities in support of combat casualty care
    3. Develop methods and approaches for implementing safe ride standards
    4. Survey and select interoperability standards.
    5. Define mission planning capabilities to coordinate patient transport

RDT&E Challenges for Evacuation on Autonomous & Unmanned Systems

MEDICAL

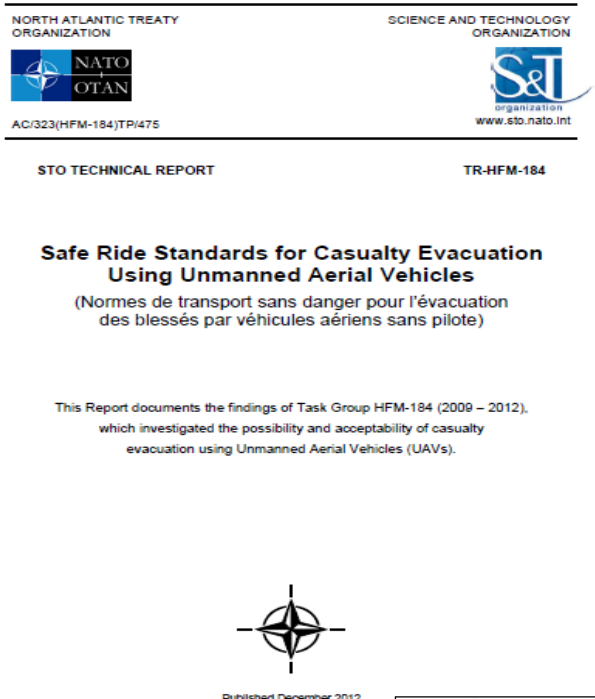
- Safe Ride Standards for UMS Transport (2012 NATO Task Group HFM-184 Study)
- Interoperability – Integration with Medical-specific equipment/capabilities – "carry on"
- En Route Care – Medic Attending vs. Remote Patient Management vs. Autonomy
- AI-based Closed Loop Critical Care Capability
- Testing, Verification and Validation

MEDICAL/NON MEDICAL

- Efficient and Safe Man-Machine/Human-UMS Interaction

NON MEDICAL

- Bandwidth & communications availability
- Cyber threat
- Autonomous/Unmanned Platform Availability
  - Need appropriately-sized multipurpose platforms
  - Air –Vertical Takeoff & Landing (VTOL)
  - Ground – multi-terrain with shock absorption



NORTH ATLANTIC TREATY ORGANIZATION

SCIENCE AND TECHNOLOGY ORGANIZATION

AC/323(HFM-184)TP/475

www.sto.nato.int

STO TECHNICAL REPORT

TR-HFM-184

Safe Ride Standards for Casualty Evacuation Using Unmanned Aerial Vehicles

(Normes de transport sans danger pour l'évacuation des blessés par véhicules aériens sans pilote)

This Report documents the findings of Task Group HFM-184 (2009 – 2012), which investigated the possibility and acceptability of casualty evacuation using Unmanned Aerial Vehicles (UAVs).

Published December 2012

Research Strategies

1. Integration of Medical Systems with general purpose UMS to include Communications & Virtual Health
2. Soft Robotics. Bio-inspired lightweight robotic manipulators based software and flexible materials
3. Multi-robot Teams and Swarms. Robot/robot teaming (eye-in-sky and rescue robot). Self assembly of small robots to perform specific missions like casualty extraction and CASEVAC
4. Unique Mobility Platforms for challenging environments. Navigate the MDB space of complex threats. Novel approaches to locomotion; rapid transformation (shape-shifters ala transformers).
5. Mission based intelligent navigation & flight controllers to implement constraints and adapt behaviors when patients are on board.

SMALL WARS JOURNAL

HOME NEWS JOURNAL SWJ BLOG FORUM EL CENTRO MAD SCIENCE

Recent Articles Current Issue Authors Archives Editorial Policy

Medical Robotic and Autonomous System Technology Enablers for the Multi-Domain Battle 2030-2050

by Nathan T. Fisher and Gary R. Gilbert

Journal Article | July 22, 2017 - 5:32pm

HOW DO WE GO FROM HERE

TO HERE?

That is our challenge

QUESTIONS?

United States Army Institute of Surgical Research

Sensory Trauma Program
Medical Effects of Directed Energy Program

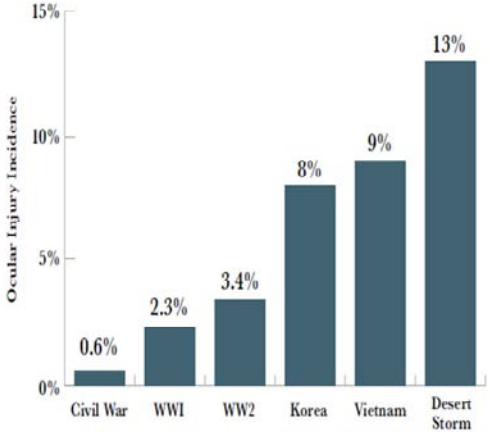
COL Carol Rymer, OD, MBA, FAAO
Department Chief, Sensory Trauma/Subtask Manager Bioeffects of DE
carol.z.rymer.mil@mail.mil

28 March 2019

The Problem

- **Combat Ocular Trauma is a significant cause of morbidity**:
  - *Past Conflicts*: World War II: 2.5-3.4%; Korean War: 4-8%; Vietnam: 9%; Persian Gulf: 13%[1]
  - *Newer Conflicts*: OEF/OIF/OND: 10% of 22,409 warfighters had COT[2]
  - 201,980 OER/OIF/OND Veterans had eye diagnostic conditions[3]
  - 2000-2010: 186,555 eye injuries worldwide; 133,275 (superficial);7,843 chemical/thermal[3]
  - 82% from IED related blasts
  - Average time from Role 3 to Role 5 = FIVE days
  - Injury Pattern (391/728): 176 Anterior Segment[4]
- **Vision is being lost** from inflammation, scarring and exposure keratopathy and creates significant pain
- Per ophthalmologists, optometrists, and combat medics there are **challenges** with current therapeutic products and **limitations** with fielded diagnostics
- **Injured patients would rather loose a limb over eyesight**

Current Medic Management



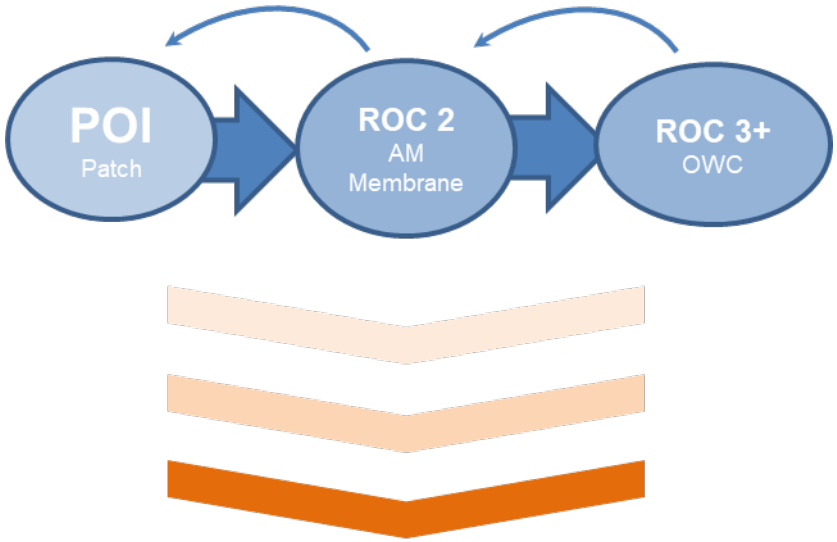
Exposure Keratopathy:
Resulting in a Corneal Ulcer & Scarring

Images courtesy Neda Nikpoor, MD

1. Ophthalmic Care of the Combat Casualty; TMM Series; 2003
2. JTTR (Sep2010)
3. VA Report:21Office of Public Health Epidemiologic Report, *Cumulative Frequencies of the Eye and Adnexa Enrollment OIF/OEF/OND* (FY October 2002 to second quarter, FY 2015).

The Impact

- Potential for high casualties predicted in the **Dense Urban Environment (DEU)** of the Modern BF
- The AM ocular bandage could mitigate corneal/conjunctival non penetrating FBs and/or burns (chemical/thermal) and return SM to duty quicker → leading to increased **Soldier Lethality**
- Stable packaged ocular bandage AM can be **pushed far forward (Pol)** in the Battlefield (BF) and can be used in **Prolonged Field Care situation (PFC)**
- Additionally – AM in a ring like device would be used in **all Roles of Care**; reducing time intensive resources of medical staff (drops v. irrigation system)
- **Reduced Evacuations** (22% due to ocular injury); **quicker RTD**
- **Early intervention to sterilize the field** yields better outcomes (OWC and/or AM with therapeutics)
- Long term **reduction in ocular scarring: inflammation; pain**
- **OWC would be used on all inpatients** to mitigate exposure keratopathy, infection, inflammation & scarring
- Longterm **economic impact**
  - 2000-10: Annual incident cost $2.3B/$25.1B – impacting VA and SS benefits, lost wages, family care[1]

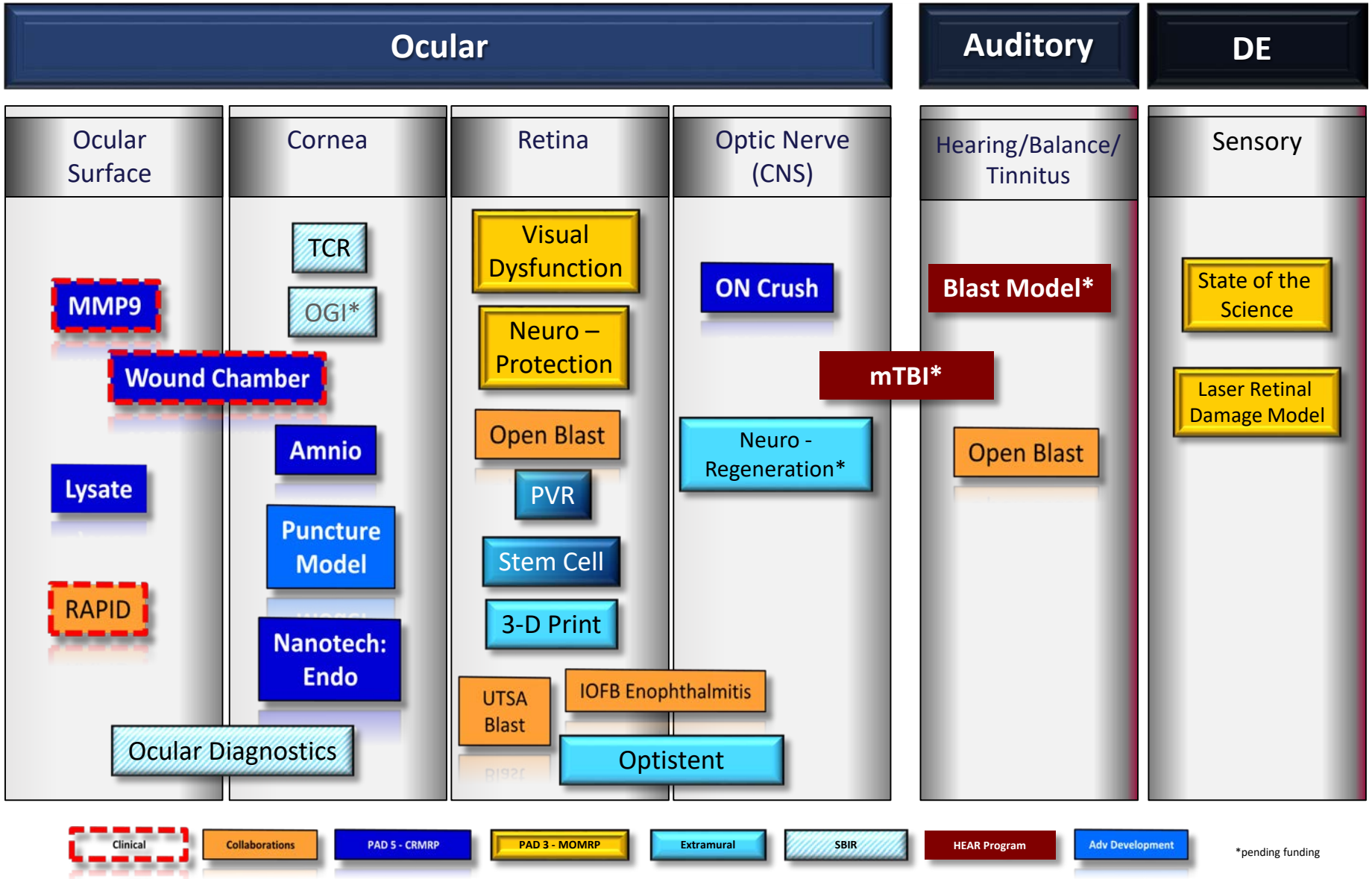


FUTURE

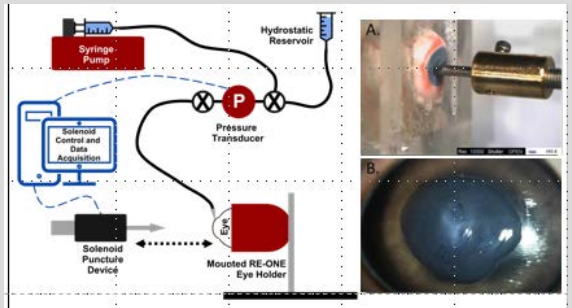
↑ Soldier Lethality
PFC Options
DE Mitigation
RTD/Reduced Evacs
Improved Outcomes

1. In 2012, the National Alliance for Eye and Vision Research released its first-ever *Cost of Military Eye Injury and Blindness* study, prepared by Kevin Frick, PhD (of Johns Hopkins University's Bloomberg School of Public Health).

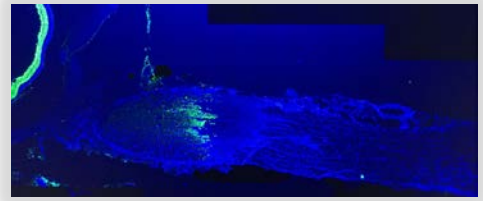
Sensory Trauma Spectrum (As of Feb2019)

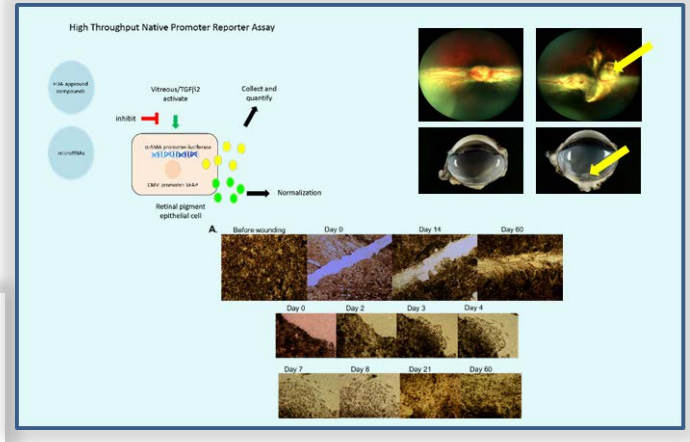


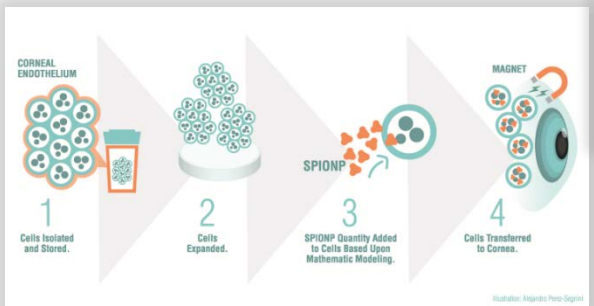
Ocular Battlefield Health & Trauma Research

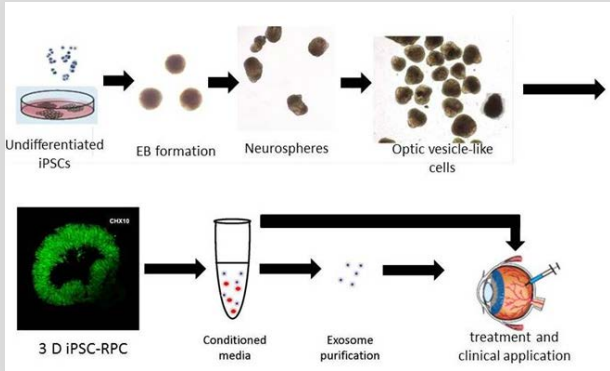


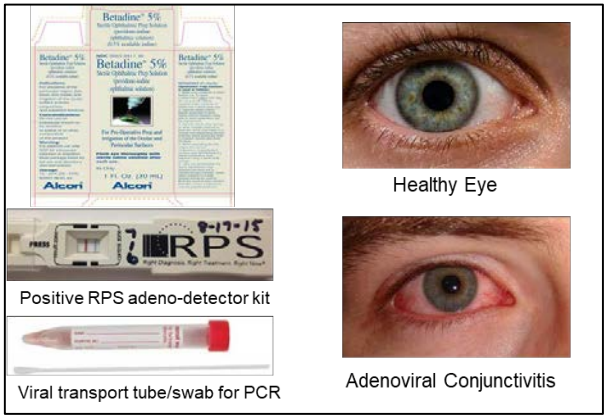
Accomplishment Highlight: Can successfully puncture the porcine cornea with different object shapes/sizes and, simultaneously, set and monitor IOP











Sensory Trauma Research Program

Development Pipeline – Current Snapshot of Functional R&D Stages

Discovery-Knowledge (6.1/6.2/6.3)
Topic Areas
TRL 1-3

- Development of animal models of ocular and acoustic injury (blast, penetrating, traumatic neuropathy, Proliferative Vitreal Retinopathy (PVR))
- Investigation of pluripotent stem cell derived products to reduce PVR
- Optic nerve regeneration
- Model development of cornea wounds for eye sealant evaluation
- Characterization of cellular injury and visual function after blast overpressure
- Detection of Inflammatory Mediator Profile in Tears

Discovery-Product (6.2/6.3)
Specific Candidate Concepts/Drugs/Devices
TRL 3-4

- Drug discovery for mitigation of fibrosis after penetrating eye injury
- Human platelet lysate topical therapeutic
- Algorithm modeling for the delivery of nano-therapeutics to the posterior surface of the cornea
- Human amniotic membrane for the treatment of corneal injuries
- Sensory trauma drug screening for stabilization , reduction, and treatment
- Early detection of open globe Injuries
- Treatment of battlefield retinal detachment via intravitreal retinal tamponade (Optistent)

Late Discovery/Transition (6.3)
Pre-clinical & Early Clinical Studies
on Selected Lead Concept/Drug/Device Expected Transition w/in 2 yrs
TRL 4-5

- Temporary Corneal Repair
- Ocular Wound Chamber (Treatment of ocular injuries including periocular burns)

Full (Clinical) Development (6.4/6.5)
Specific Product
TRL 5-9

- TBD

Knowledge Products To Support Clinical Practice

- New guidelines for use of ocular wound chamber
- New guidelines for temporary corneal repair
- CPG Update for Ocular betadine for adenovirus disinfection treatment (RAPID)

Go/no go decision gate

Description

Mission – Identify & characterize biological effects resulting from new and emerging lethal and non-lethal DE weapon systems in order to support the development of DE countermeasures.

Overarching Lines of Effort

- Understand effects of DE at the cellular/tissue level in living models
- Identify assessment and diagnostic techniques to correlate with physiological changes

Why JBSA?
Geographical Center of Synergy & Expertise

- **United States Army Medical Research and Materiel Command**
  - **US Army Institute of Surgical Research (USAISR)**
    - **Leader in Combat Casualty Care Research with state of the art facilities, resources, and subject matter experts in all medical disciplines. Access to providers and DOD's only Burn Center.**
  - US Army Aeromedical Research Laboratory (USAARL)
  - Biotechnology High Performance Computing Software Applications Institute (BHSAI)
  - US Army Institute of Environmental Medicine (USARIEM)
- **DoD Partners DE Bioeffects Research**
  - TSRL: USAF 711 Human Performance Wing
    - Human Effectiveness Directorate – Dr. Stephanie Miller/Lt Col Christopher Putnam
      - Radio Frequency Radiation Branch (RHDR) - Dr. Gordon Hengst
      - Optical Radiation Effects (RHDO) – Dr. Benjamin Whitmore
  - USAF 59th Medical Wing
    - Dr. Deborah Niemeyer, Chief Scientist
  - Naval Medical Research Unit – San Antonio (NAMRU-SA)
    - Dr. Sylvain Cardin, Research Director
- **Other DoD Non-Medical Research Programs**
  - US Army Research Lab (ARL)
  - Air Force Research Lab (AFRL)
  - Office of Naval Research (ONR)
  - Joint Non-Lethal Weapons Directorate

Alignment with CSA's Modernization Priorities

(1) Long-range Precision Fires

- Guidance will inform the safe use of laser and DE weapons technologies for the user and understand collateral damage on the target.

(2) Next-generation Combat Vehicles

- Guidance will inform DE protection and injury mitigation requirements

(3) Future Vertical Lift Platforms

- Guidance will inform DE protection and injury mitigation requirements

(5) Air and Missile Defense

- Guidance will inform the safe use of laser and DE weapons technologies for the user and understand collateral damage on the target.

(6) Lethality

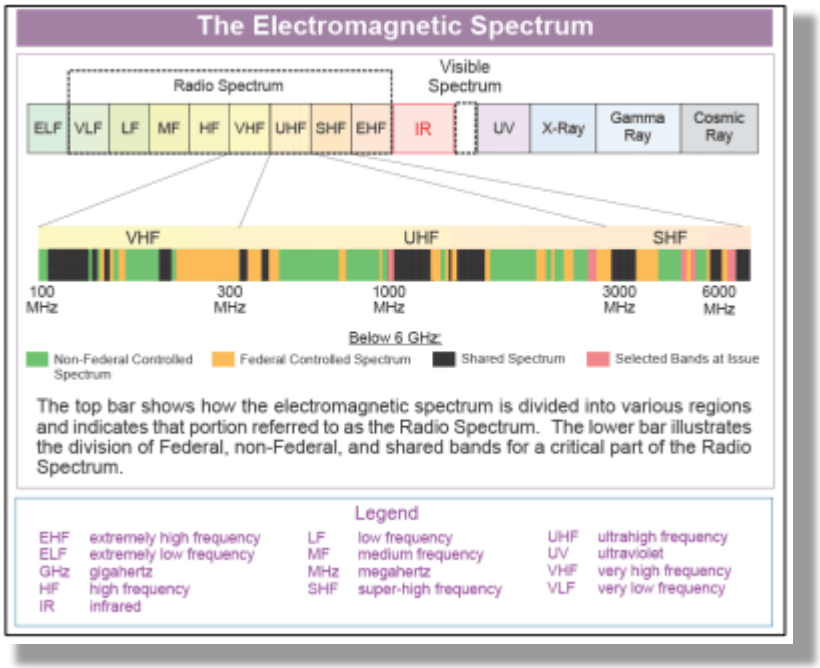
1. Training – Guidance will inform safe use of DE weapon systems in training and mitigation strategies for Army medicine.
2. Soldier Protective Equipment – Guidance will inform protective equipment requirements
3. Cognitive and Psychological Performance – Guidance will inform performance effects from non-lethal and lethal DE technology exposures
4. Prolonged Field Medical Care – Guidance will inform diagnostic and injury mitigation capabilities

Impact on Soldier Health & Readiness

Many nations, friend & foe, are developing DE weapon systems for counter-material, -sensor, & -personnel uses on the battlefield. Deployment of these systems will increase the risk of exposure & injury to Warfighters. Tissue or organs affected depend on wavelength or frequency of EM radiation emitted.

As a result, we must prepare for a variety of DE injuries.

- Radiation in the visible and near IR wavelength is hazardous to the retina.
- The mm wavelength regions used by ADS is a burn threat because it is absorbed within a few mm's of the skin.
- Other frequencies or wavelength can penetrate deeper, jeopardizing organs, the CNS, or the skeleton.



Impact on Soldier Performance

Directed Energy injuries are a <u>direct threat to military lethality</u>, limiting Soldier enhancement, performance and resilience in an austere environment.

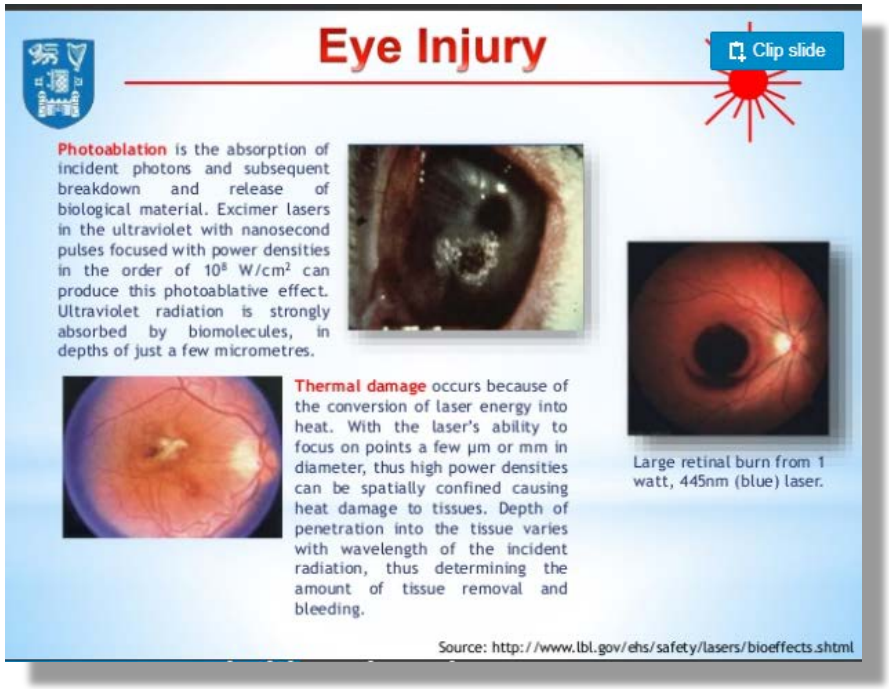
- DE systems are currently fielded for non-lethal (NL) applications to include hand-held lasers such as those used in Escalation of Force procedures to warn or dazzle approaching vehicles and personnel.
- In the near future it is anticipated that allies and enemies will begin using weaponized DE technology.
- Increase in energy/power output, miniaturization of components, and the development of frequency-agile systems will allow vehicle-mounted lethal-DE weapons to become available for counter-materiel, counter-sensor and counter-personnel uses on the multi-domain battlefield within the next decade.
- The deployments of these systems will undoubtedly increase the probability of exposure and potential injury to Warfighters and civilians.

Figure 3. Prototype Army Active Denial System (ADS)

Source: Lauren Poindexter, "ARDEC Engineers Develop Solid State Active Denial Technology for Non-Lethal Crowd Control, *U.S. Army*, October 12, 2016.

Long-Term Impact on Soldier Quality of Life

It is expected and anticipated that DE injuries can lead to devastating long term sensory degradation in function that can impact quality of life.



- It is likely that laser engagements will be used directly against our forces, and their effects on the health and mission performance of our service members will be of particular concern.
- The weaponization of lasers to produce eye injury is a real and present danger to our deployed Soldiers

Prevalence

The growing number of practical applications of laser energy has resulted in a dramatic increase in laser use in our daily lives. Military, industrial, medical and recreational uses of lasers have steadily expanded. Accidental laser eye injuries are common.

- Severity depends upon the laser frequency, duration of exposure and the amount of energy absorbed by the retina
- A published study of data gathered from ten representative cases of laser eye injury occurring in the U.S. military between 1984 and 2000 described patients who suffered retinal damage, without corneal injury. Most were caused by accidental exposure to a Q-switched, Neodynium:YAG (Nd:YAG) laser at 1064 nm wavelength, the most common laser with efficient atmospheric transmission.
- As laser retinal burns may be painless and the damaging beam sometimes invisible, they can be misdiagnosed. Such misdiagnosis has medical and financial consequences.
- Since it is probable that most medical personnel in the field have limited experience dealing with patients who have had a laser exposure, a more complete understanding of laser-induced injury of the retina will provide guideline for accurate diagnosis and treatment.

Effectiveness

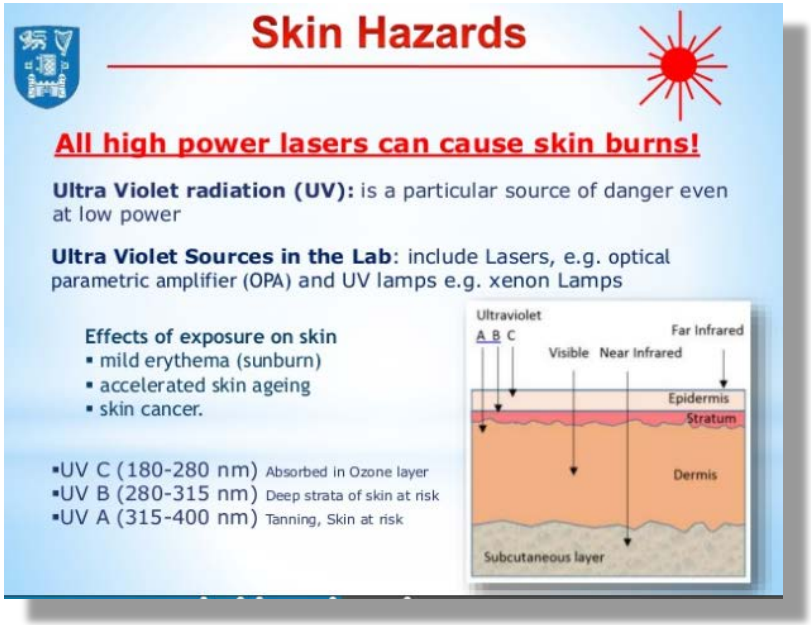
The types of injuries caused by these weapons will be novel to current medical personnel. Research will close the following gaps:

- Lack of **knowledge** of acute and chronic injury caused by directed energy exposure
- Lack of **data** to provide medical guidelines for protection from emerging directed energy weapons
- Lack of medical **countermeasures** against emerging directed energy threats
- **Impact** of directed energy exposure on medical equipment and wearable sensors

- USAISR in collaboration with other MRMC laboratories and sister services will be developing a DE Center of Excellence
- Guiding principles
  - Maintain tech watch and situational awareness of technological breakthroughs/ challenges in DE
  - Anticipate DE threats in 2025 and beyond
  - Minimize investigative redundancy across Services
  - Foster synergistic relationships with USAF/ USN

*DE Bioeffects Working Group Meeting, 26 July 2017
All gaps address **Army Modernization Priority: Soldier Lethality

Practicality



As DE weapons begin to proliferate on the battlefield, there will be a need for medical interventions to protect against injuries caused by these weapons. **There are currently no prophylactic interventions to protect against DE injuries.** However, there may be neuroprotective drugs that, can limit tissue damage. One example is that there are potential drugs that can protect retinal tissue and preserve retinal function, against laser exposure. The same paradigm may be used to protect against sonic exposures which may cause hearing loss, tinnitus and vestibular dysfunction. There is a need to investigate medical products that can be taken before exposure to protect tissue, or reduce severity of tissue damage, from DE exposure.

Injury Prevention & Readiness related to DE Projects

Retinal Damages by Suprathresholds of Q-switched Neodymium-Yag Laser Exposures in Swine

- **Aim 1:** Define Suprathresholds of 1064-nm Q-switch Nd-Yag Laser Exposures with in vivo dose-response studies.
- **Aim 2**: Select the suprathresholds of 1064-nm Q-switch Nd-Yag laser to investigate the pathohistology of retinal damage during different time course.

State of the Science of DEW - Evaluation of Current & Emerging DE Threats in the Joint environment to include HEL & RF Bioeffects & a Review of Tri Service Databases on DE Injury

- **Aim 1:** Understand State of the Science; current threat & current Triservice Research in Bioeffects of DE
- **Aim 2**: Prepare and deliver a State of the Science Workshop on Bioeffects of DE and classified and unclassified DEW and JNLDEW.

Operator Health Hazards and Bioeffects Following Exposure to Acoustic Directed Energy Threats

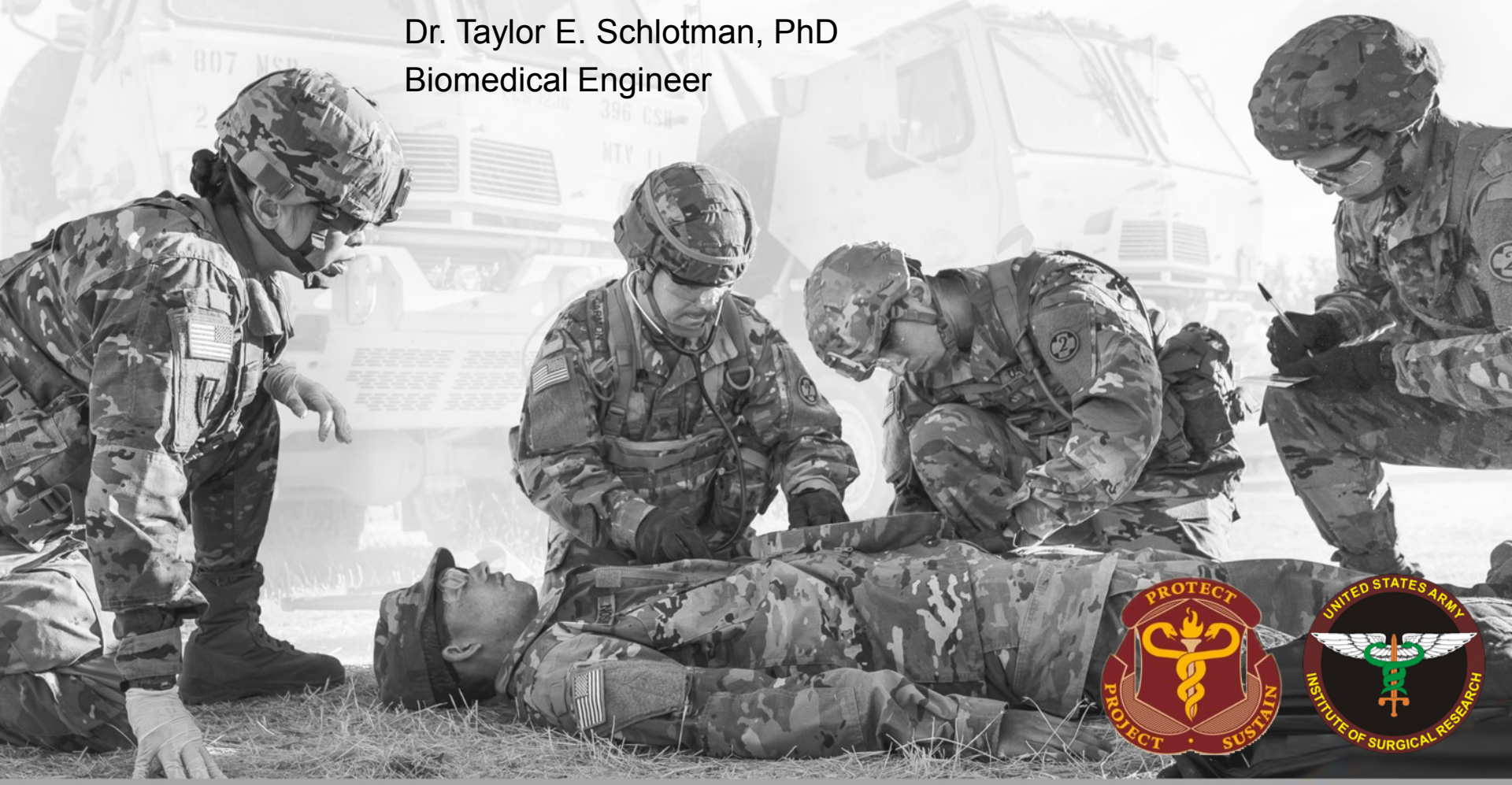
- **Aim 1:** To evaluate the risk of injury to the Warfighter caused by acoustic directed energy threats, such as flash bang grenades and/or long range acoustic hailing devices and the impact on operational performance
- **Aim 2:** To develop criteria for protective equipment and safety guidelines

Establish injury criteria for lethal/non-lethal whole-body human exposure to directed energy

- **Aim 1:** Establish quantifiable whole-body, injury-risk criteria for human exposure to lethal/non-lethal directed energy (DE)
- **Aim 2:** Establish medical guidelines for the safe use of DE systems

Battlefield Health & Trauma Center for Human Integrative Physiology

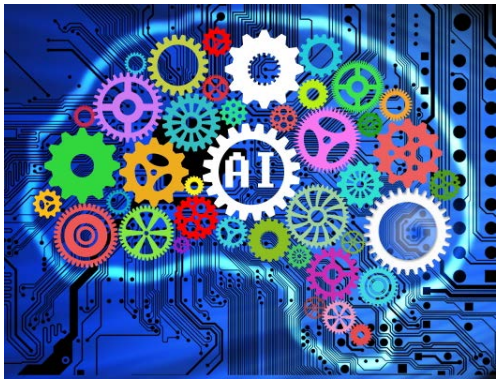
Dr. Taylor E. Schlotman, PhD
Biomedical Engineer

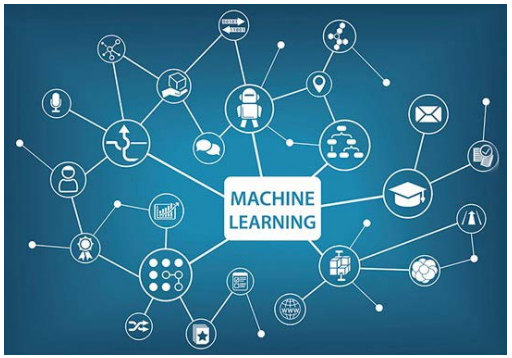


No Disclosures

The opinions or assertions contained herein are the private views of the presenter and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense

What's The Big Idea?





- » Data are NOT about statistics, machine learning, etc.
- » Data are about **<u>understanding</u>**

- » *Understand* your problem
- » *Understand* your data

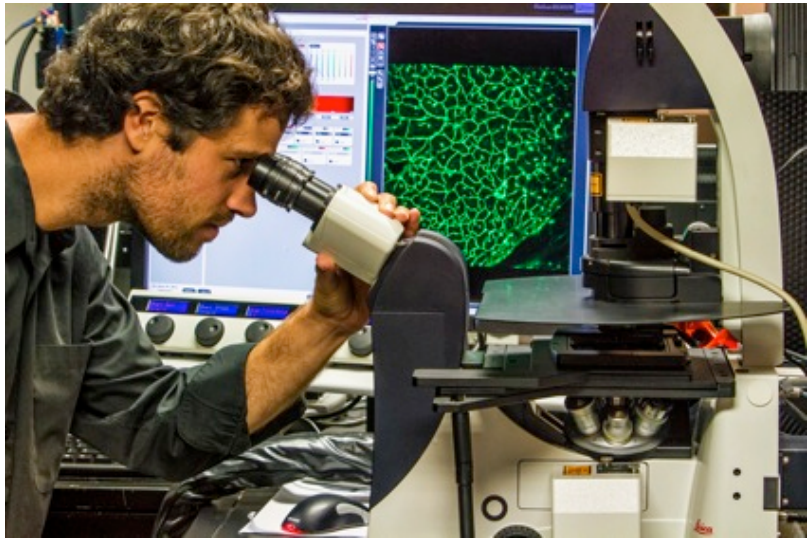
Collecting the *RIGHT* Data

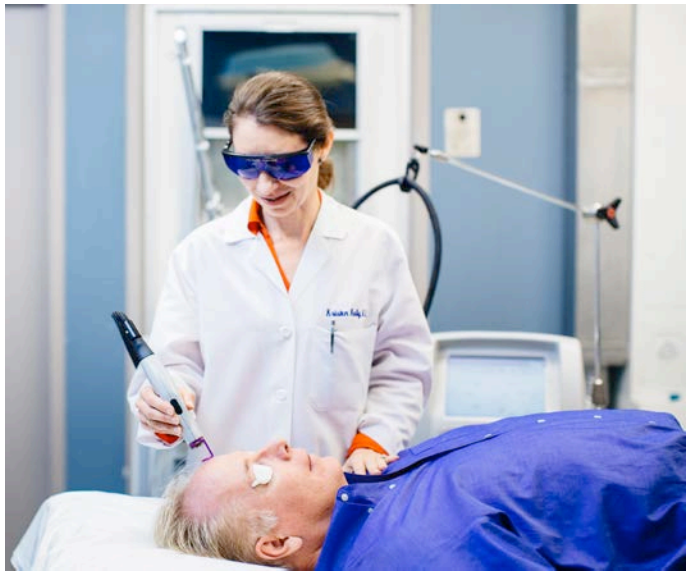
Just because the path is well trodden does not mean that you are headed in the right direction."

– Anonymous

Research Vision

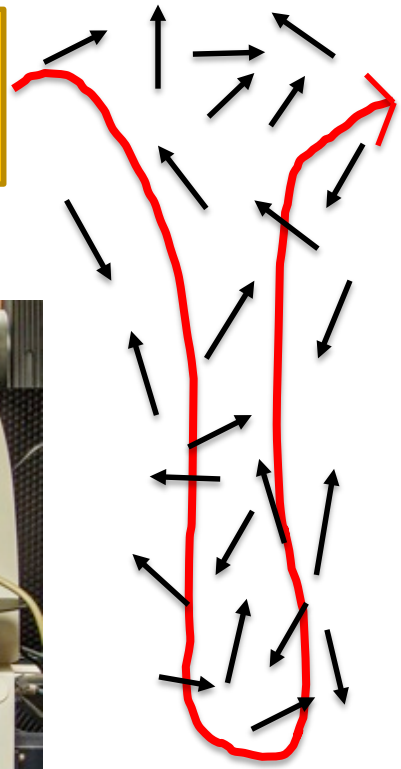
Basic Science and Technology Development → Clinical Diagnostics and Therapeutics



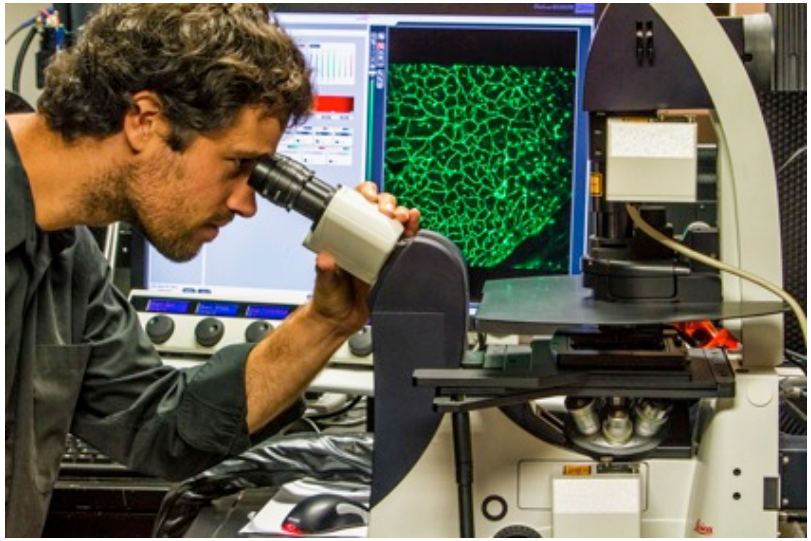


The Reality of Research

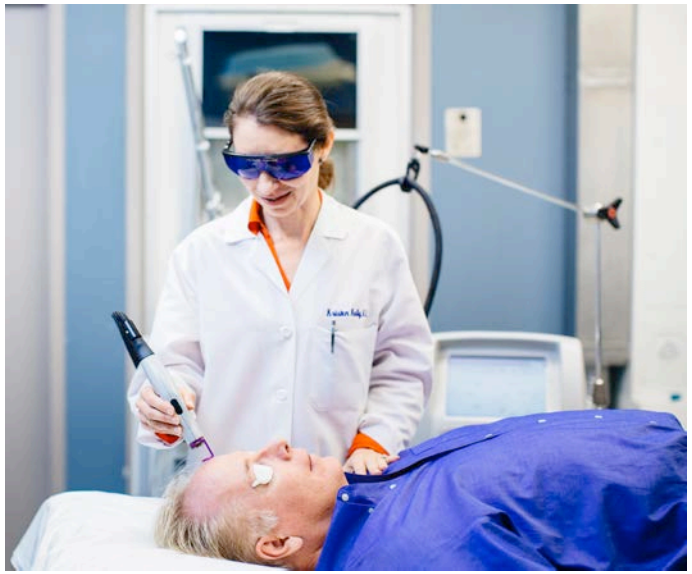
Basic Science and Technology Development



Clinical Diagnostics and Therapeutics



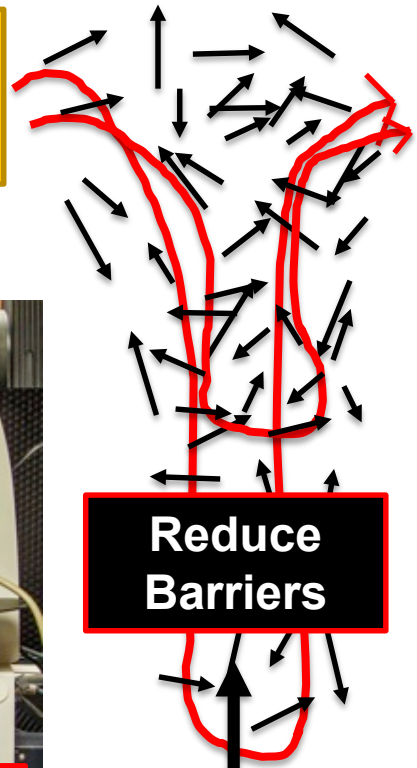
BARRIERS

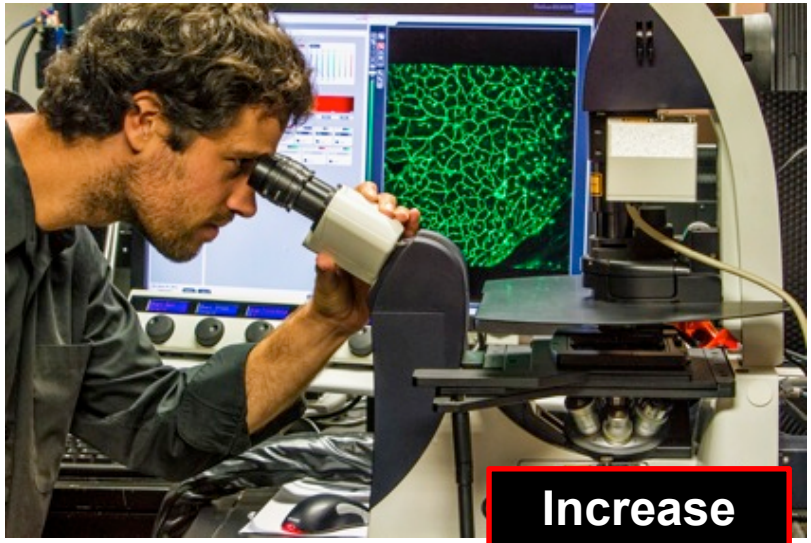


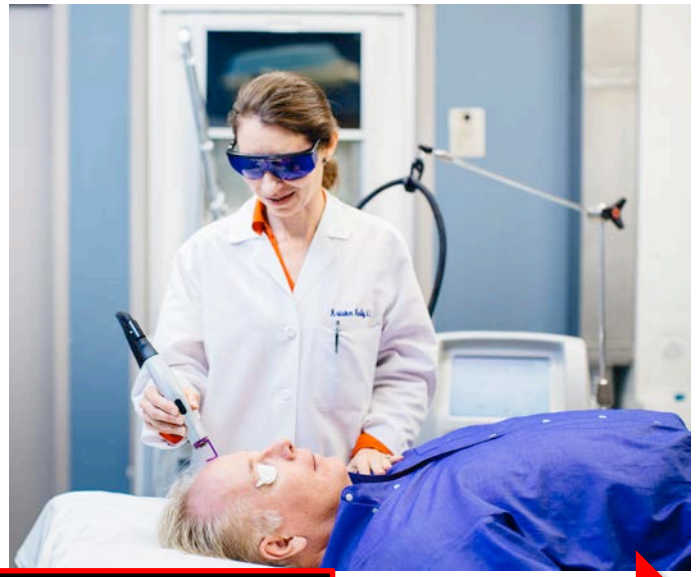
The Goal: Shift Equilibrium to RIGHT

Basic Science and Technology Development

Clinical Diagnostics and Therapeutics







Reduce Barriers

BARRIERS

Increase Activity

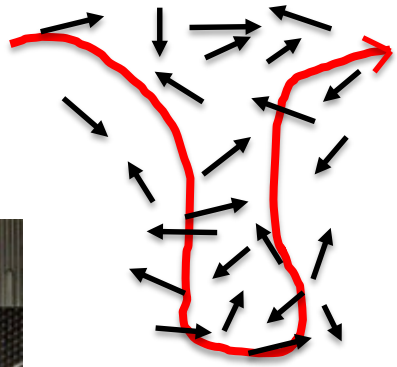
Accelerate translation, validation, commercialization

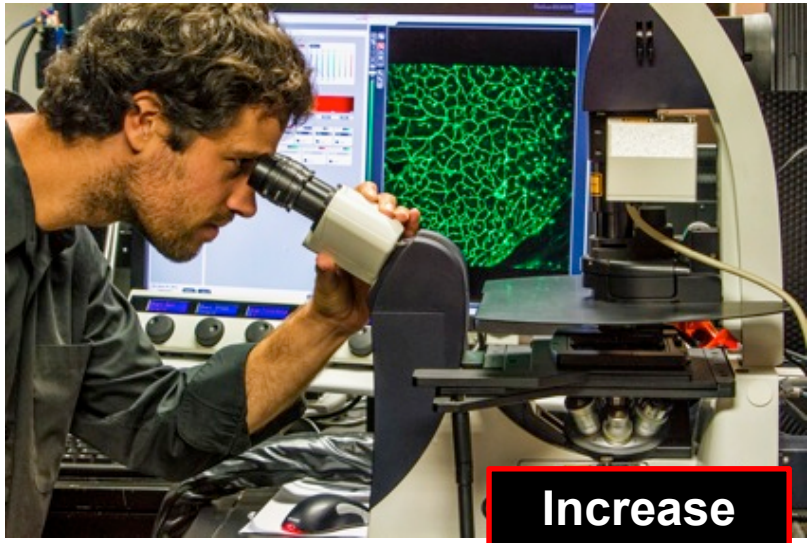
National Institute of Biomedical Imaging and Bioengineering

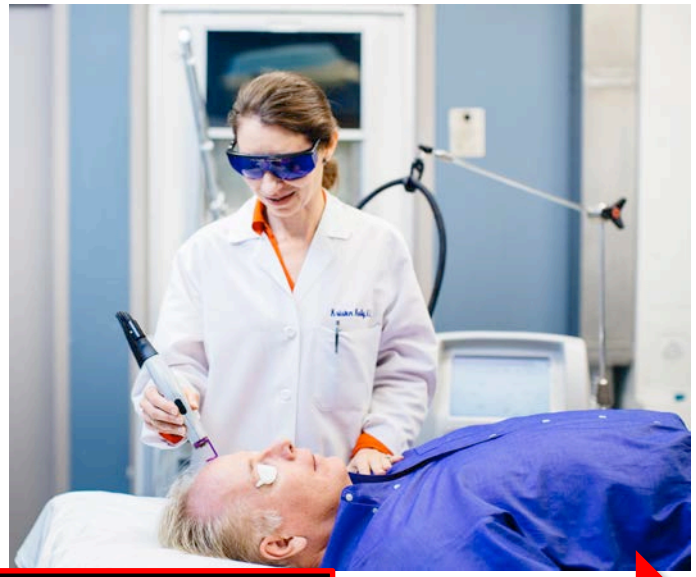
Bridge the gap: CHIP – Industry Partnerships

Basic Science and Technology Development

Clinical Diagnostics and Therapeutics







Reduce Barriers

Increase Activity

Accelerate translation, validation, commercialization

National Institute of Biomedical Imaging and Bioengineering

CHIP - Industry Partnerships: FDA-cleared Technology

2003-2007:
2 Impedance Threshold Devices

2017:
Impedance Threshold Device for Ventilator

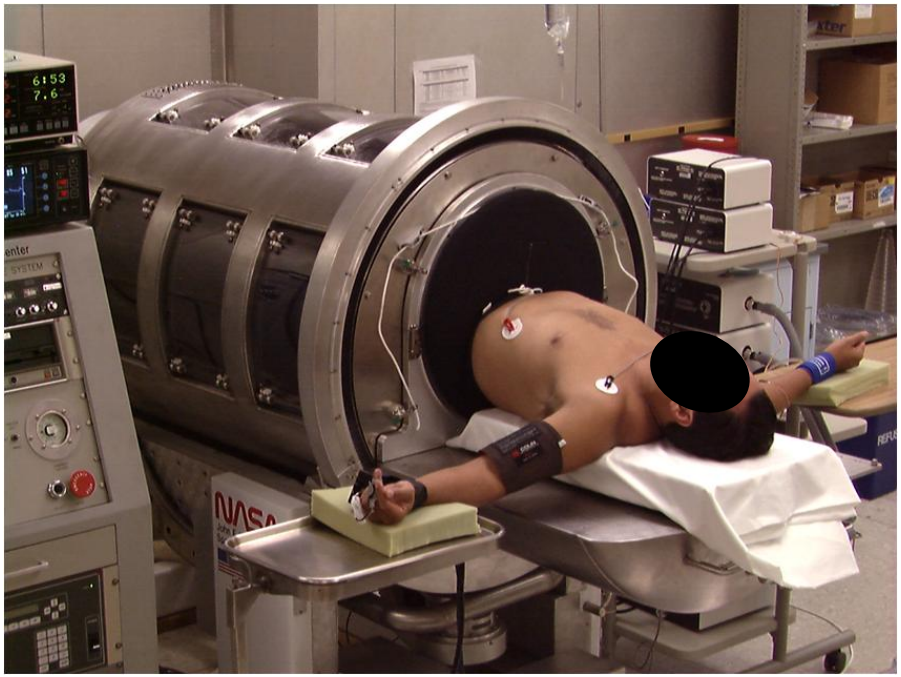
2003 → 2006 → 2009 → 2012 → 2015 → 2018 → 2019

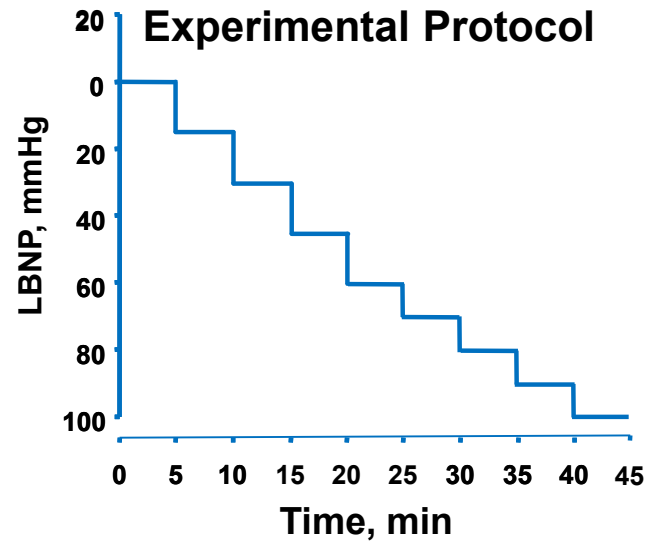
2012-2014:
2 Near Infrared Spectroscopy (NIRS) Devices

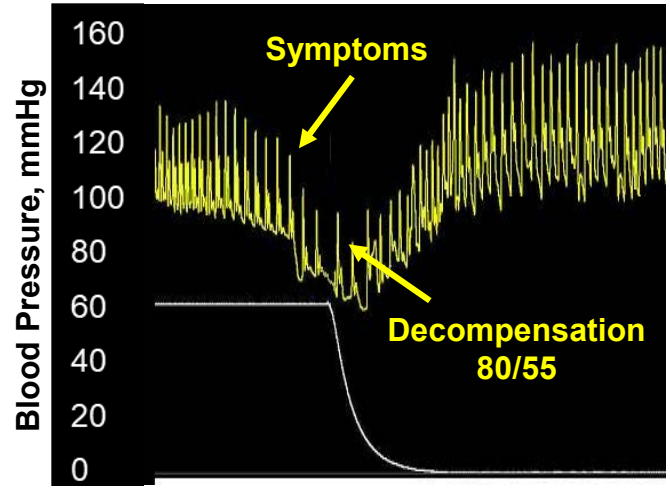
2012:
Vital Signs Monitor

2016-2018:
2 Medical Monitors for Compensatory Reserve

Human Model of Hemorrhage: Lower Body Negative Pressure (LBNP)







FDA qualification under Medical Device Development Tools (MDDT) program

Cooke et al, *J Appl Physiol* 96:1249-1261, 2004

Industry Collaboration with LBNP Research: The Compensatory Reserve

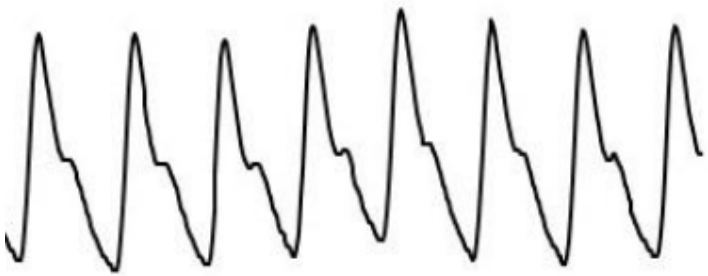
With the Mayo Clinic:
Anticipated FDA-clearance of Compensatory Reserve Measurement (CRM) Algorithm for assessment of tissue oxygen debt

- » Collection of arterial waveforms during **LBNP**
  - » Subjects taken to **decompensation**
- » CRM algorithm built using **machine-learning**
  - » Analyzes changes in **arterial waveform features**
    - » Represents full integration of **all compensatory mechanisms**
- » **Prec** [illegible] cal status in ***individual*** patients in **real time**

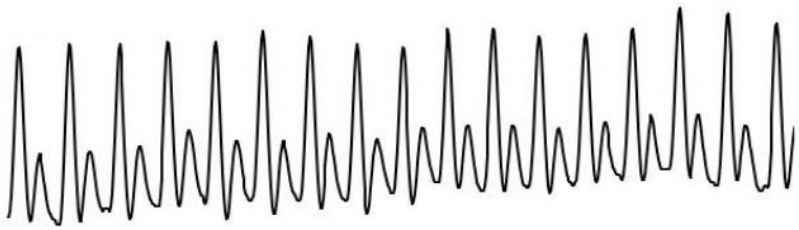
COLLECTING THE RIGHT DATA FOR THE PROBLEM

Future Work: Becoming Diagnostic

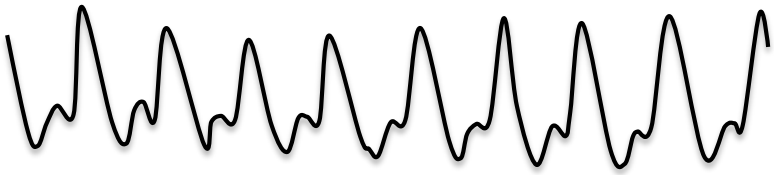
Normal



Hemorrhage



Sepsis



Tension Pneumothorax

Thank you.

PROTECT
PROJECT
SUSTAIN
UNITED STATES ARMY
INSTITUTE OF SURGICAL RESEARCH