



Clinical and Rehabilitative Medicine Research and Development Program

MILITARY MEDICINE PARTNERSHIP DAYS
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Director, Clinical and Rehabilitative Medicine Research Program

US Army Medical Research and Materiel Command

24 March 2015





Purpose and Outline



PURPOSE: To increase understanding of the Military Research and Development needs in Vision, Hearing, Balance and Pain

OUTLINE:

- Overview of Clinical and Rehabilitative Medicine Research Program
- Pain Research Program
- Hearing and Balance Research Program
- Vision Research Program
- Regenerative Medicine Advanced Development Needs



The views expressed in this presentation are those of the author(s) and may not reflect the official policy or position of the Department of the Army, Department of Defense, or the U.S. Government.

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Program Areas



SENSORY SYSTEMS (Vision, Hearing, Balance)

Visual, auditory, and vestibular dysfunction associated with traumatic injury
Conduct research and development to provide treatments to restore and rehabilitate sensory system dysfunction

PAIN MANAGEMENT (Battlefield, Acute, Chronic)

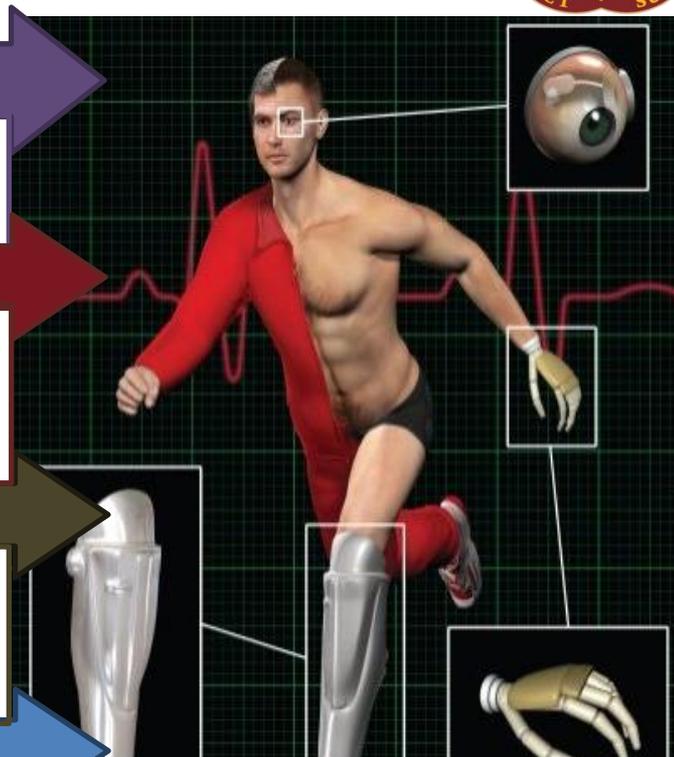
Management of pain ranging from the point of injury to chronic pain management
Conduct research and development to provide improved methods, drugs, and devices for the management of pain at all levels of care

REGENERATIVE MEDICINE AND TRANSPLANTS

Extremity and craniomaxillofacial injuries, burns and scarless wound healing, Hand and face transplants, genitourinary lower abdominal reconstruction
Reconstruct or regenerate damaged or missing cells, tissues or organs to establish normal function

NEUROMUSCULOSKELETAL INJURY

Prosthetics, orthotics, spinal cord injury, and orthopedic injury rehabilitation
Conduct research and development to provide products and information solutions for diagnosis, treatment, and rehabilitation after neuromusculoskeletal injuries



There are many strategies . . .
but only ONE goal.



Mission: *To ethically and responsibly implement long-term strategies to develop knowledge and materiel products to reconstruct, rehabilitate, and provide definitive care for injured Service Members. The ultimate goal is to return the Service Member to duty and restore their quality of life.*



Panel Members



- **LTC Scott Griffith, M.D.**, Pain Consultant to the Army Surgeon General, Director of NCC Pain Management Fellowship and National Capital Region Pain Initiative
- **Kurt Yankaskas**, Noise-Induced Hearing Loss Program Officer, Office of Naval Research
- **COL Jeffrey Cleland, O.D.**, Ocular Trauma & Vision Restoration Program, US Army Institute of Surgical Research
- **Melanie Eacho**, Product Manager, US Army Medical Materiel Agency
- **Kristy Pottol**, Director, Tissue Injury and Regenerative Medicine Program Management Office, US Army Medical Materiel Development Activity





Clinical and Rehabilitative Medicine Research Program Pain Management Portfolio

MILITARY MEDICINE PARTNERSHIP DAYS

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Scott R. Griffith, MD

LTC, MC, USA

Walter Reed National Military Medical Center

24 March 2015



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Panel Member



LTC Scott R. Griffith M.D.

- Pain Subspecialist, Walter Reed National Military Medical Center
- Pain Management Consultant to the Army Surgeon General
- Program Director, NCC Pain Management Fellowship
- Director, National Capital Region Pain Management Initiative





Pain Management Portfolio



- **Task Goal**

- Provide products and information solutions for the diagnosis and alleviation of battlefield, acute and chronic pain and sequela

- **Task Description**

- The Pain Management Research and Development program includes DoD efforts for the management of pain ranging from the point of injury to chronic pain management with a view spanning basic research through clinical development



Pain Scientific Steering Committee Prioritized Capability Gaps (1 of 4)



- **Inadequate alternatives to current opioid analgesics for severe pain management by the medic/corpsman on the battlefield/remote locations**
 - Lack of a morphine/fentanyl alternative that has a significantly improved safety profile
 - Lack of a morphine/fentanyl alternative with minimal cognitive effects
- **Inadequate strategies for management of chronic pain under the care of a clinician in non-deployed settings**
 - Inadequate preventative treatments for conversion of acute to chronic pain
 - Lack of knowledge of patient outcomes following chronic pain management treatment
 - Inadequate treatments for chronic pain management
 - Limited strategic communication approaches for educating providers, patients, family members, and unit leaders





Pain Scientific Steering Committee Prioritized Capability Gaps (2 of 4)



- **Inadequate identification of pain generators**
 - Inadequate predictors of treatment responses and outcomes
 - Inadequate objective assessment and diagnostic tools for pain
 - Inadequate predictors of individual pain intensity
 - Inadequate knowledge of the pathophysiology of pain mechanisms and implications for treatment
- **Inadequate acute pain management in deployed locations, including battlefield and resource-limited environments**
 - Inadequate knowledge of effects of multimodal treatments of acute pain on patient outcomes
 - Lack of clinical practice guidelines (CPGs) for best practices for assessment and management of acute pain
 - Inadequate knowledge of effects of time to treatment of acute pain on patient outcomes
 - Inadequate mobility of anesthetics and analgesics and associated monitoring requirements



Pain Scientific Steering Committee Prioritized Capability Gaps (3 of 4)



- **Inadequate strategies for identifying and addressing biopsychosocial aspects of pain**
 - Inadequate strategies to manage the impacts of sleep, nutrition, and exercise on pain
 - Inadequate knowledge and strategies for empowering the patient for pain management (and prevention)
 - Inadequate knowledge of family and social dynamics on pain management
 - Inadequate knowledge of the impacts of co-morbidities associated with chronic pain
 - Inadequate knowledge of resilience and vulnerability factors influencing pain outcomes
- **Inadequate strategies for management of acute pain under the care of a clinician in non-deployed settings**
 - Inadequate knowledge of the relationship between experiencing acute pain and the development of chronic pain syndrome
 - Inadequate treatments for acute pain
 - Inadequate preventative pain treatments



Pain Scientific Steering Committee Prioritized Capability Gaps (4 of 4)



- **Inadequate chronic pain management in deployed locations, including battlefield and resource-limited environments**
 - Inadequate knowledge of the operational utility of chronic pain management far-forward
 - Lack of clinical practice guidelines (CPGs) for best practices for assessment and management of chronic pain
- **Inadequate substance misuse and abuse assessments and treatments in pain management**
 - Inadequate knowledge of the risk factors unique to the military population related to pain medication misuse/abuse/diversion/addiction
 - Inadequate knowledge of the best practices for treatment of chronic opioid therapy (COT) complications such as dependence and addiction





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Research Success



- **Battlefield Pain Management**
- **MS-B February 2015, 3 Phase 3 studies 2015, 1 Contract and 1 CRADA**
- **What is it?**
- **Sufentanil Nanotab System**
 - Successfully completed a phase I/II clinical trial of patients following bunionectomy surgery. The difference in pain for 30 mcg sufentanil-treated patients and for placebo-treated patients was statistically significant ($p=0.003$). Phase 3 studies to start 2015.
 - Oral Transmucosal Ketamine: Completion of a phase I/II clinical trial of patients following tooth extraction. Phase 3 studies to start 2015.
- **Significance**
 - Rapidly acting products designed to relieve acute pain with minimal side-effects usually associated with the use of common analgesics currently in use. These products are meant primarily for use in the Tactical Field Care and Tactical Evacuation Care phases of Tactical Combat Casualty Care (TC3) and at ROC-1.





Clinical and Rehabilitative Medicine (CRM) Hearing & Balance Restoration Portfolio

MILITARY MEDICINE PARTNERSHIP DAYS
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Kurt Yankaskas

Noise-Induced Hearing Loss Program Officer

Office of Naval Research

24 March 2015





Purpose



To increase understanding of the **CRM Hearing & Balance Research Portfolio**.

- **Scope**
 - The Hearing and Balance Traumatic Injury Restoration and Rehabilitation portfolio includes DoD efforts in the areas of hearing and vestibular dysfunction associated with traumatic injury, with a view ranging from basic research through clinical development.
- **Purpose**
 - Restore/rehabilitate the hearing and balance of Service Members post-traumatic injury by advancing medical capabilities (improved methods, drugs, and devices) through research and development





Hearing, Tinnitus and Balance



Hearing and Balance Capability Gaps

- Inadequate ability to restore hearing
- Inadequate ability to treat hearing loss
- Inadequate ability to prevent and/or treat tinnitus
- Inadequate ability to prevent/treat vestibular dysfunction

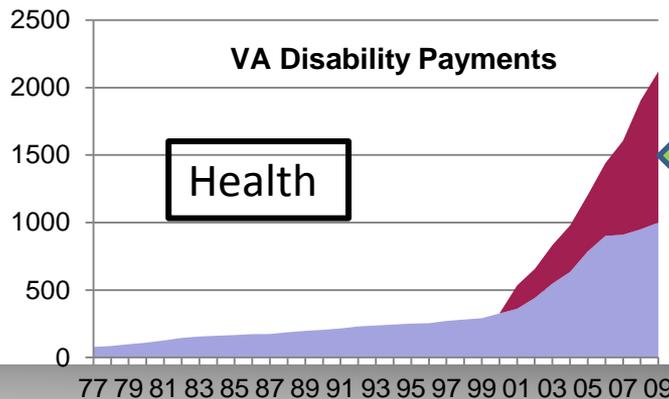
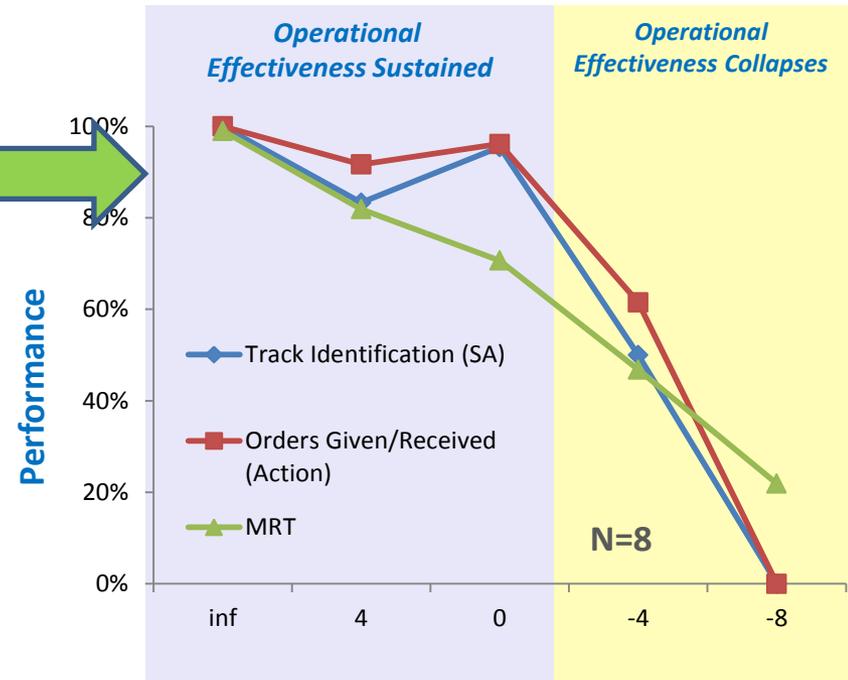
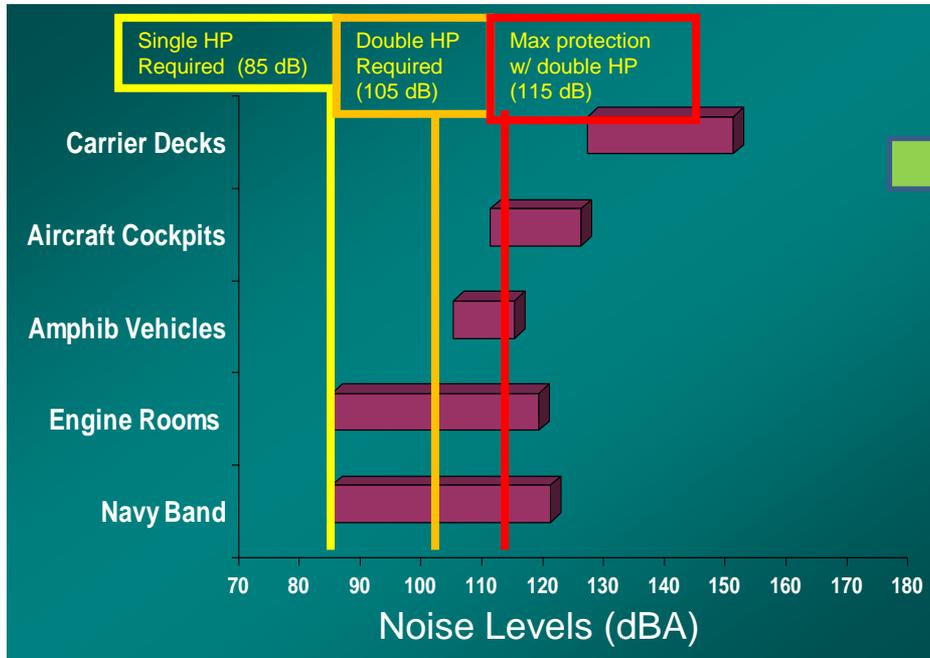




Noise-Induced Hearing Loss

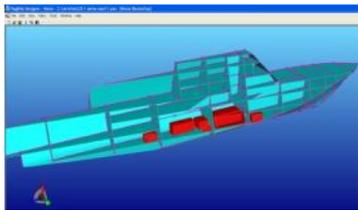


Hazardous Noise Exposures Impact

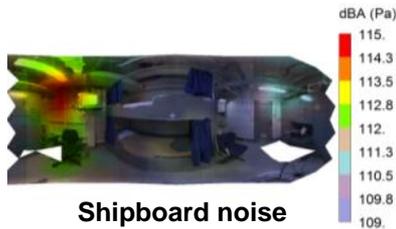


Systems Approach for an Integrated 6.1 / 6.2 / 6.3 Program

Source Noise Reduction

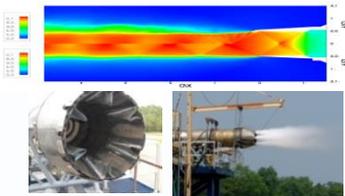


Shipboard noise assessment



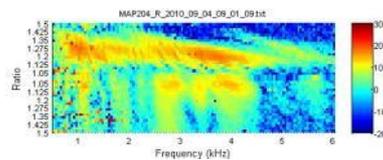
Shipboard noise path validation

Jet noise Reduction



Laboratory modeling/ scale tests of jet noise reduction

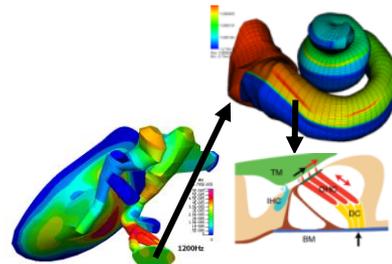
Incidence, Susceptibility & Evaluation



Assessment tools

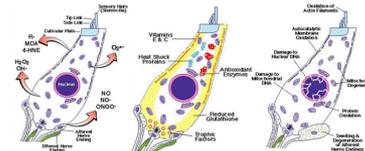


Hearing loss simulator



Modeling Tools

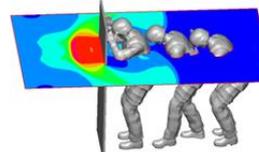
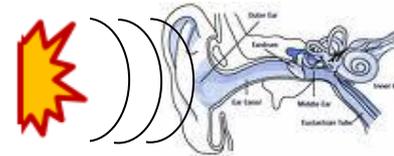
Medical Prevention & Treatment



Cell regeneration

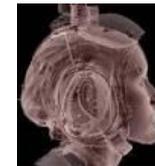


Pharmacologic interventions and drug delivery



Blast interventions

Personal Protective Equipment (PPE)



Shipboard PPE



3D Digitization for "Prescription" Ear Plugs



In-Ear Dosimetry

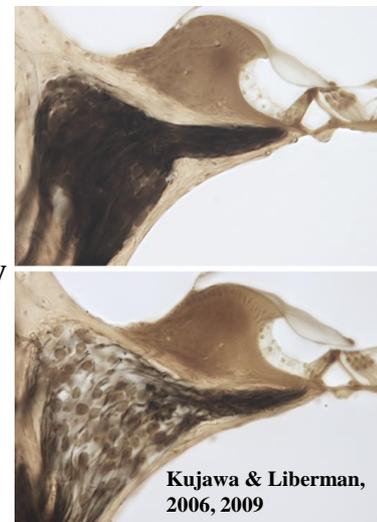


Underwater comms & hearing protection

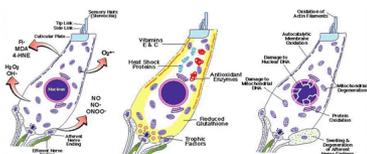
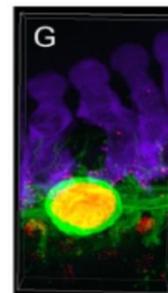
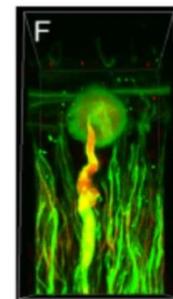


FY08 – 14 Achievements:

- Hair cell regeneration in neo-natal mouse - 2010
- Hair Cell regeneration via support cell differentiation - 2013
- Initiated nerve cell regeneration 2012
- Pharmaceutical investigations –
 - NAC, ebselon - 2010
 - NAC toxicology studies for clinical trials - 2013
- Investigation in mission performance with NIHL
- Next generation low-power cochlear implant technology 2012
- Blast modeling for “Breechers”
 - model utilized cross Service -2013
- Identification of NIHL susceptibility markers via USMC study
 - ID'd 17 genes not previously reported, 2013
 - Analysis of metabolic pathways 2013
 - Focus drug efficacy – 2014
- Pharmaceutical pathway efficacy - 2013



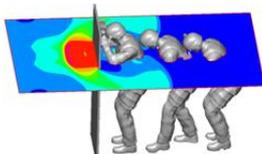
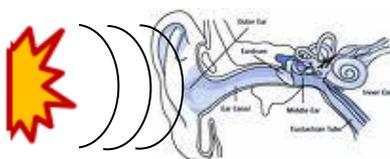
Kujawa & Liberman, 2006, 2009



Cell regeneration



Pharmacologic interventions and drug delivery



Blast interventions

Continued research in:

- Tinnitus etiology
- Potential tinnitus assessment technique
- Nerve cell regeneration
- Auditory Pathway Imaging (YIP)



Biomarkers: NIHL/Tinnitus susceptibility



Description: NIHL/tinnitus biomarkers are unresolved.

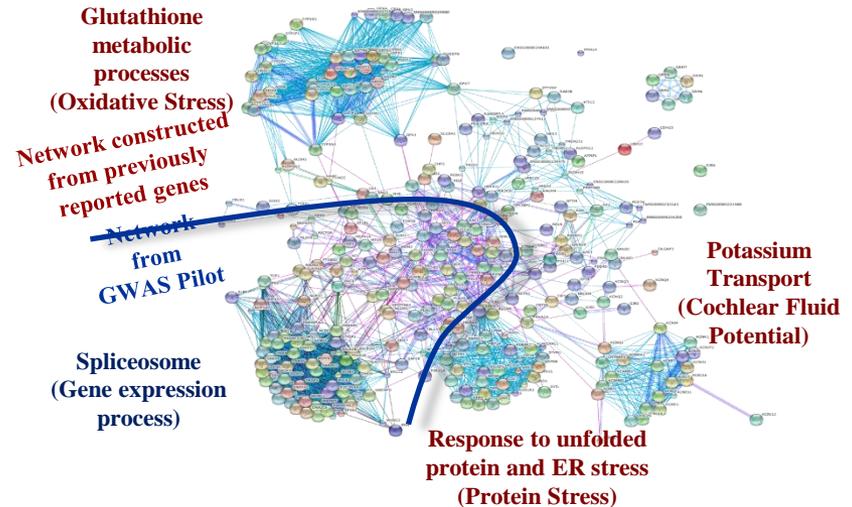
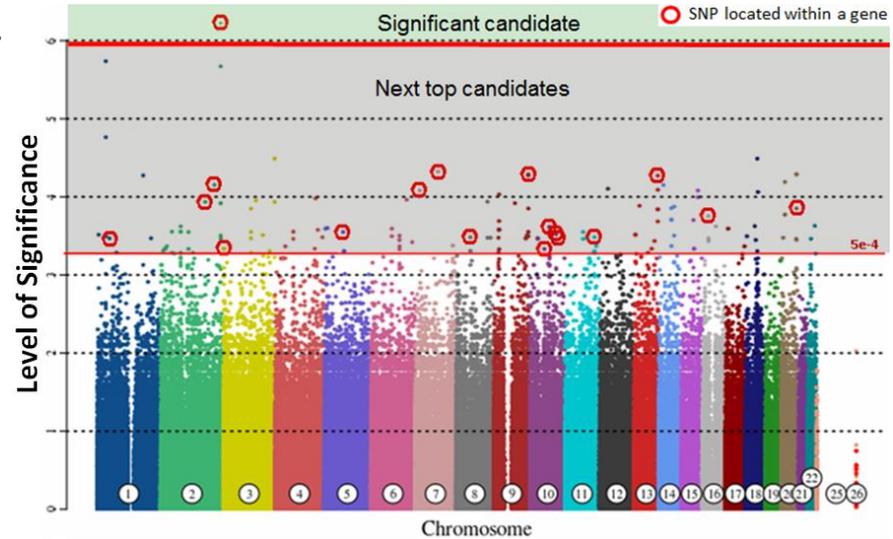
- Therefore, individual susceptibility is indeterminate
- Metabolic pathway analysis widely used to study pharmaceutical interactions indicates efficacy for compound interaction and may serve as a susceptibility indicator

Naval Need: There are no clear indicators for NIHL/tinnitus susceptibility in pervasive 24/7 noise exposures and is a co-morbidity in mTBI

FY14 Accomplishments:

- NAC toxicology studies for clinical trials
- Identification of NIHL susceptibility marker via USMC study, Identified 17 genes not previously reported
 - Analysis of metabolic pathways
 - Focus drug efficacy

Impact: The identification of NIHL/tinnitus risk groups will enable focused hearing health strategies thus improving Warfighter performance in high noise environments and reducing long-term hearing injury/tinnitus disabilities.





Clinical and Rehabilitative Medicine (CRM) Research Program Vision Restoration Portfolio

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COL Jeffrey M. Cleland, O.D., Director
Ocular Trauma & Vision Restoration Program,
US Army Institute of Surgical Research
US Army Medical Research and Materiel Command
24 March 2015





Purpose



To increase understanding of the CRM Vision Research Portfolio.

- Scope

- *The Vision Traumatic Injury Restoration and Rehabilitation portfolio includes DoD efforts in the areas of visual dysfunction associated with traumatic injury, with a view ranging from basic research through clinical development.*

- Purpose

- *Restore/rehabilitate the vision of Service Members post-traumatic injury by advancing medical capabilities (improved methods, drugs, and devices) through research and development*





Vision Capability Gaps



Vision Capability Gaps

- Mitigation and treatment of traumatic injuries, war-related injuries, and diseases to ocular structures and the visual system
- Mitigation and treatment of visual dysfunction associated with TBI
- Ocular and visual systems diagnostic capabilities and assessment strategies
- Vision rehabilitation strategies and quality of life measures
- Vision restoration





Ocular Trauma Research Program



- **Mission (Purpose):** Advance treatments, methods and modeling that protect, repair and restore the eye and vision from injuries sustained by our Warfighters in the defense of our nation.
- **Vision (Goal):** Be our Nations answer to the challenges faced in the detection and treatment of combat related eye and vision disorders.





Ocular Trauma Research Program



Trauma

- Blast Induced Injury Characterization
- Ruptured Globe-AM & Rose Bengal
- Inflammation Control-Proteinomics
- Wound Chamber

Product Development

- Wound Chamber
- SCCO2 Amniotic Membrane
- Nanoparticle development
- Amnio platform with drug delivery
- HgH film (Extended Release Rx)



Model Development

- Cornea: Burn/ Exposure/ Infection
- Blast-Induced Injury (Rabbit/Rat/Pig)
- PVR

Tissue Regeneration

- Cornea: AM & Stem Cells
- Cornea: HGH Delivery
- Retina: iPS Stem Cells





Research Success



PROBLEM:

Current ocular wound dressings on the market

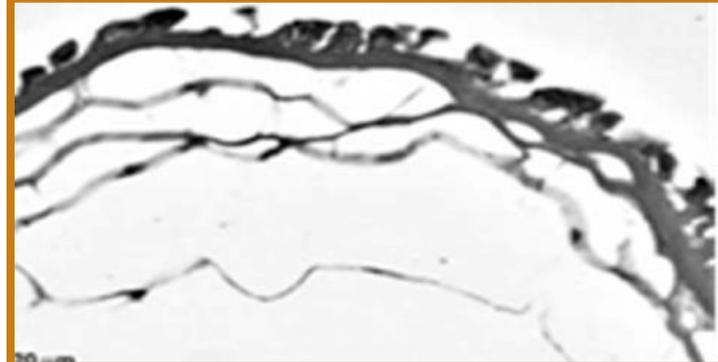
- Address minimal needs of the damaged ocular surface
- Lack the potential to facilitate scarless wound healing and tissue regeneration
- Commercially available amniotic membranes cannot be stored at room temperature

CAPABILITY GAP: Mitigation and treatment of traumatic injuries, war-related injuries, and diseases to ocular structures and the visual system

NEED: for a product that can address not only these basic needs, but also provide such other useful aspects such as biocompatibility, infection control, bioactive molecule delivery, therapeutic cell delivery, all while acting as a bioscaffold matrix.

PROPOSED SOLUTION: To utilize a novel method Super Critical Carbon Dioxide to process AM which maximizes the therapeutic properties of AM and develop an “off the shelf” sterile, decellularized, cost-effective product that will provide a 3-dimensional extracellular matrix to promote corneal repair and treat other ocular wounds with drug loading potential.

Amniotic Membrane sterilized using gamma irradiation shows degradation of the extracellular matrix



Histological analysis of SCCO₂-treated amniotic membrane shows equal or better collagen retainement than other commercially available products



SCCO₂

AMNIOGRAFT

EPIFIX





Clinical and Rehabilitative Medicine (CRM) Advanced Development in Vision

MILITARY MEDICINE PARTNERSHIP DAYS
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Melanie Eacho, PhD, RAC

US Army Medical Materiel Agency

US Army Medical Research and Materiel Command

24 March 2015





US Army Medical Materiel Agency



- **Mission:** To develop, tailor, deliver, and sustain medical materiel capabilities and data in support of readiness and healthcare operations globally.
- **Vision:** Lead the acquisition and sustainment of medical materiel equipment and technology.





Purpose



To increase understanding of the CRM Vision Advanced Development efforts.

- Capability Gaps

- *Mitigation and treatment of traumatic injuries (e.g. blast, burn, laser, penetrating etc.) to ocular structures*
- *Early intervention and mitigation strategies to reduce injury and slow or stop loss of vision*





Temporary Corneal Repair Capability

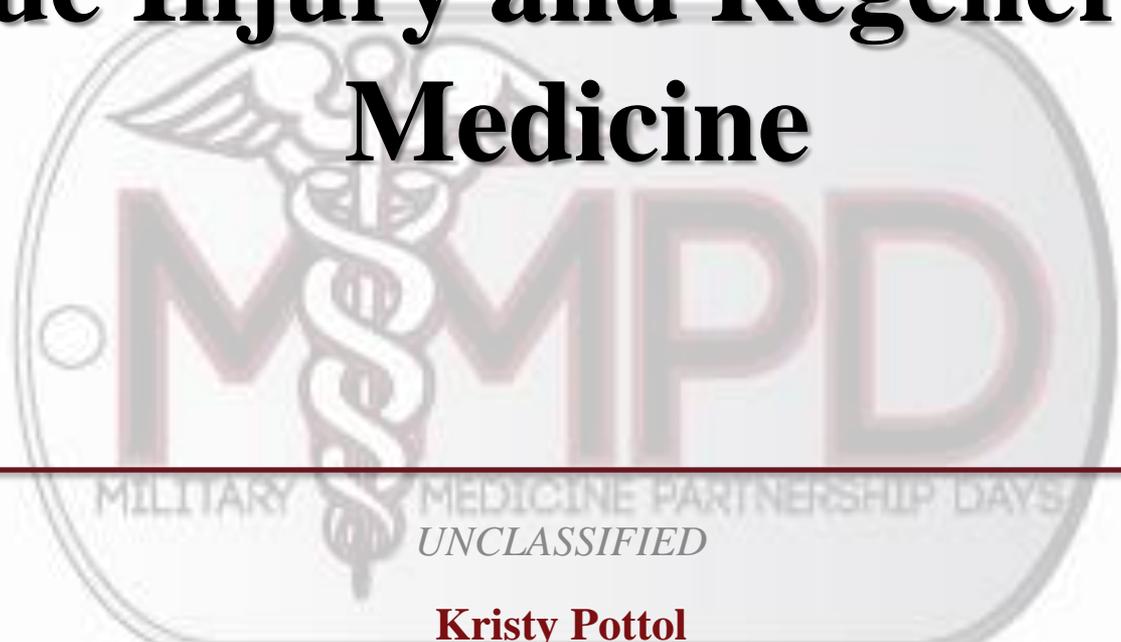


1. Indication: temporary corneal closure and stability following eye trauma
 - *For use by trained ophthalmologists and other physicians*
 - *For use in far forward care as possible (Role of care 2 and above)*
2. Characteristics:
 - *FDA cleared/approved (threshold)*
 - *Provide ocular stability/reduce inflammation to maximize corneal transplant success*
 - *Serve as a ocular drug delivery platform*
3. Joint services effort





Tissue Injury and Regenerative Medicine

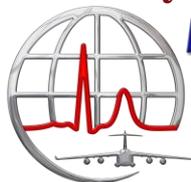


Kristy Pottol

**Tissue Injury and Regenerative Medicine
Project Management Office**

US Army Medical Research and Materiel Command

24 March 2015



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Tissue Injury and Regenerative Medicine



To build industrial capacity, reduce barriers to entry, and decrease cost of goods sold for:

- *Regenerative medicine*
- *Prosthetics / orthotics*





Key Objectives

1. Enabling technology for regenerative medicine

- *Tissue preservation*
- *Chain of custody*
- *Standardized panel of assays*

2. Lowering the barrier of entry for prosthetics / orthotics

- *Common interface compatibility*
- *Modular to accommodate size or component upgrades*
- *Improve power and leverage other common industrial standards*
- *Ruggedize prosthetics and orthotics for return to duty*





Questions?



For additional questions after the conclusion of the conference, send an email message to usarmy.detrick.medcom-usamrmc.mbx.mmpd@mail.mil

