Infectious Diseases and Military Operational Medicine (Environmental Health, Injury Prevention, Physiological Health and Psychological Health)

US Army Medical Research and Materiel Command

19 April 2016

Panel Members

- COL Michael P. Kozar (Co-Chair) – Science & Technology
- LTC Bryan T. Gnade – Advanced Development
- LCDR Christopher Steele (Co-Chair) – Science & Technology
- Mr. Steve Hawbecker – Advanced Development

Infectious Diseases

Colonel Michael P. Kozar, Ph.D

Director, Military Infectious Diseases Research Program

US Army Medical Research and Materiel Command

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Military Infectious Diseases Research Program RDT&E

Mission

To conduct for the Department of Defense, a focused and responsive world class infectious diseases research and development program leading to fielding of effective, improved means of protection and treatment to maintain maximal global operational capability with minimal morbidity and mortality

- Force Health Protection
- Naturally occurring, known, predictable threats
- Requirements driven

Mission and Functions

Plan, coordinate and oversee a DOD Science and Technology (S&T) program that develops effective and improved countermeasures to minimize the impact of naturally occurring endemic infectious diseases upon the warfighter.

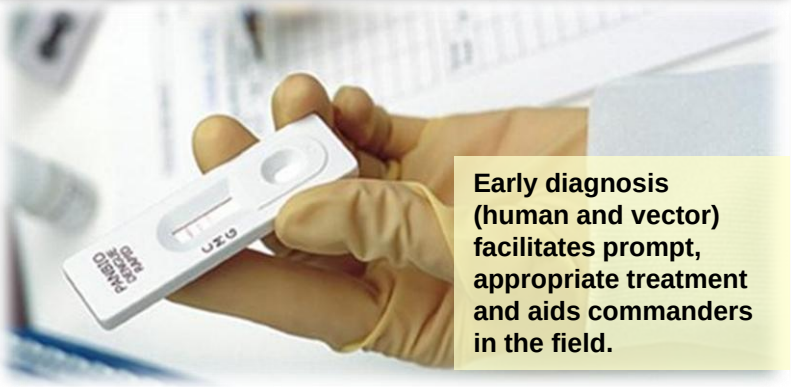
Prevention

- Infectious diseases adversely impact military operations. Vaccines are the long-term solution.

Treatment

New drugs are continually required to overcome evolving drug resistance.

Diagnostics



Early diagnosis (human and vector) facilitates prompt, appropriate treatment and aids commanders in the field.

Insect Vector Control

Most militarily relevant infectious diseases are transmitted by biting insects and other arthropods.

What Makes the MIDRP Unique?

- Focused on FDA/EPA approved products for adult indications
  - Enhance global health security
  - Enhance stability operations
- USAMRMC organized like a pharmaceutical company
  - Product development oriented organizational structure and processes
  - Decision Gate System integrates best industry business practices
  - Historical success of vaccines/therapeutics
- Core research program embedded in Military labs with uniformed researchers
  - Discipline and mission focus
  - Global research platform – Host nation partners
  - Unique overseas clinical trial sites

Infectious Diseases Countermeasure Development Strategy

	Prevention	Field Interventions	Long Term Treatment/ Management
Points of Use	• Pre Exposure/Pre-Deployment	• Deployed in the Field	• MTF/Definitive Care
Capability Need	• Provide Immunity Before Exposure	• Reduce Risk of Exposure to Pathogens • Reduce Risk of Illness (LDD) • Identify Agents	• Reduce Exposure to Nosocomial Pathogens • Identify Agents of Wound Infections • Optimize Wound Infection Management
Research Solutions	• Understand Epidemiology, Pathophysiology, and Immunity • Develop and Test Candidate Products	• New Drugs • Vector Control Products • Blood Screening Tools • Human Diagnostics – Vector Detection	• New Drugs and Biologics • Diagnostics • Environmental Decontamination Products • Bio-Marker Discovery
Products	• Malaria Vaccine • Dengue Vaccine • ETEC Vaccine • HIV Vaccine • HFRS Vaccine	• Improved Bed Net • Tafenoquine • IV Artesunate • Non-DEET Repellants • Topical Paromomycin • Leishmania Rapid Diagnostic Device	• Anti-Microbial Human Skin Substitute • Sideromycins - Antibacterial Delivery Systems • Arbekacin • MDRO Real-time Diagnostics

Investment Strategy

Tier 1 - High user need, High operational risk

Disease
Malaria (all types)
Diarrhea - bacterial
Dengue fever
Chikungunya/Onyong-nyong, Ross River Fever
Norovirus
Mers-CoV and other Emerging Inf. Diseases
MDR Bacteria
Ebola hemorrhagic fever/Marburg
Influenza

Active MIDRP Effort

Vaccine, prophy or treatment available

Select Agents

Strong National/Global Effort

Tier 2 - Medium user need, Medium operational risk

Disease
HIV/AIDS
Leishmaniasis - cutaneous and mucosal -visceral
Hantavirus hemorrhagic fever with renal syndrome/pulmonary syndrome
Adenovirus
Leptospirosis
Schistosomiasis
Typhoid/paratyphoid fever
Meningococcal meningitis
Rabies
Crimean-Congo hemorrhagic fever
Q fever
Lassa fever
Rift Valley fever
Melioidosis
Tuberculosis w/MDR included
West Nile fever

Conduct of Chemical And Biological Defense Program

50 U.S.C. § 1522 (d)(2) "Funding requests for the program may not be included in the budget accounts of the military departments.

Intramural Overseas Research Laboratories

Critical Resource in Global Infectious Disease Research

USAMRIID, Fort Detrick

NAMRU-3, Cairo

WRAIR/NMRC, Silver Spring

AFRIMS, Bangkok

USAMRU-K, Nairobi

NAMRU-6, Lima

USAMRU-G, Tbilisi

NMRC-Asia, Singapore/
NAMRU-2, Cambodia

Program Portfolio

	Research Effort	Advanced Development	Fielded Products
Parasitic Diseases	• Malaria drug (CDD) • Malaria vaccine (CDD) • Leishmaniasis	• Intravenous Artesunate (CPD) • Tafenoquine • Topical Paromomycin drug (CPD)	• Atovaquone/Proguanil (Malarone®, 2000) • Doxycycline (Vibramycin®, 1992) • Halofantrine (Halfan®, 1992) • Mefloquine (Lariam ®, 1989) • Sulfadoxine-Pyrimethamine (1983) • Chloroquine-Primaquine Tablets (1969) • Primaquine (1952) • Chloroquine (1949)
Viral Diseases	• Dengue (CDD) • Hemorrhagic fevers • Scrub Typhus • HIV Global (CDD) • Acute respiratory disease research • Chikungunya vaccine development	• Dengue Tetravalent (CDD) • HIV Regional (CDD)	• Adenovirus 4 & 7 (1980) – (2011) • Japanese Encephalitis - cell based (2009) • Hepatitis A (1995) • Japanese Encephalitis (1992) • Hepatitis B (1981)
Diagnostics Development	• Point-of-need devices (CDD) • Biofire Filmarray NGDS assay development • ESKAPE pathogens,	• Biofire Filmarray NGDS - Malaria, Dengue, Chikungunya	• Malaria Rapid Diagnostic Test (2007) • Leishmania Rapid Diagnostic Device (2014) • 5 hour antimicrobial susceptibility testing transitioned to industry (Accelerate Diagnostics) Expect FDA aproval in 2017

Program Portfolio

	Research Effort	Advanced Development	Fielded Products

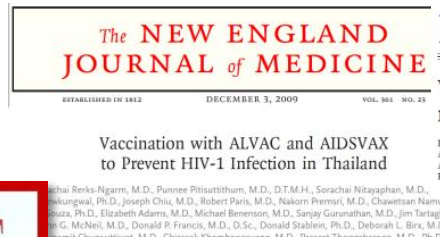
Bacterial Diseases	• Clinical studies using current antibiotics for the prevention of infection post surgery
	  • Intrasite vancomycin
	  • Bismuth-thiol
	• Preclinical studies with novel therapeutic agents for the treatment of wound infections
	  • Broad-spectrum conjugate vaccine
	  • Gallium citrate
	  • Antifungal (VT-1598)
	  • Recombinant interleukin-12
	  • Activated adult mesenchymal stem cells
	• Preclinical studies with novel anti-infective delivery systems for the treatment & prevention of wound infections
	  • Anti-infective human skin substitute
	  • Antimicrobial nanoemulsion (NB-201)
	• Diarrheal (CDD)
		• Rapid Microbiological Diagnostics for MDRO Quantitative Identification	• Antimicrobial Prescribing Practices - Prevention of Infections Associated With Combat-Related Injuries (series of publications. *J. Trauma* 2011)
			• Arbekacin (FDA-approved for Single site study at Walter Reed National Military Medical Center)
			• Recognition and Comprehensive Management of Invasive Fungal Infections in War Wounds - JTTS Clinical Practice Guideline approved 1 Nov 2012
			• Meningococcus (A, C, Y, W-135) (1981)
			• Oral Live Typhoid Ty21A (1989)
			• Sentrex BioSponge™ - added to FSS 1 Apr 2015

Vector Ctrl & Radio-protection	• Repellents/Insect control • Insect identification • Arthropod-Vector Detection Device (CDD)	• Bednet • CO2 Generator Mosquito Trap • AV-RDD Chikungunya Virus	• Combined Camo Face Paint (2013) • Alternate Repellent System (2013) • Arthropod Vector Rapid Detection Device for Dengue (2012) • Rift Valley Fever virus Vector Detection Assay (2011) • West Nile Virus detection Kit (2001) • Amifostine (Ethyol®, 1995) • DEET-based Insect Repellent (1946)

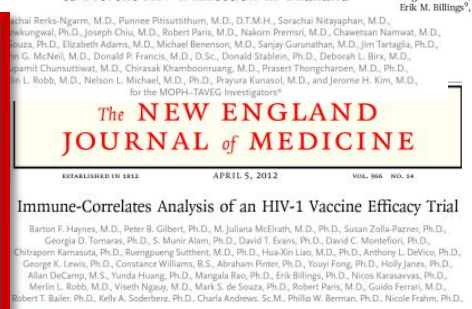
Success Continues Today

USAMRMC PLAYS KEY ROLE IN THE CURRENT LEADING VACCINES DEVELOPMENT

- HIV
  (TIME 2009 -Top 10 Medical Breakthroughs)
- Malaria
  (Time 2011 - Top 10 Medical Breakthroughs)
- Dengue


The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 DECEMBER 3, 2009 VOL. 361 NO. 23

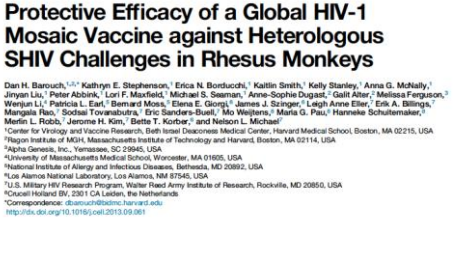
Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

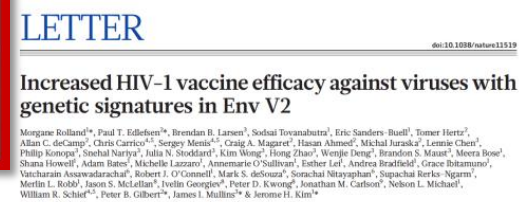

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 APRIL 5, 2012 VOL. 366 NO. 14

Immune-Correlates Analysis of an HIV-1 Vaccine Efficacy Trial


LETTER
doi:10.1038/nature10766

Vaccine protection against acquisition of neutralization-resistant SIV challenges in rhesus monkeys


Protective Efficacy of a Global HIV-1 Mosaic Vaccine against Heterologous SHIV Challenges in Rhesus Monkeys


LETTER
doi:10.1038/nature11519

Increased HIV-1 vaccine efficacy against viruses with genetic signatures in Env V2

RESEARCH ARTICLE

Protection Against Malaria by Intravenous Immunization with a Nonreplicating Sporozoite Vaccine


The NEW ENGLAND JOURNAL of MEDICINE

The PfSPZ Vaccine (cryopreserved radiation-attenuated sporozoites)
- Safe, very well tolerated
- 100% protection in the subjects that received the highest vaccine dose

gsk

GSK's malaria candidate vaccine, Mosquirix™ (RTS,S), receives positive opinion from European regulators for tl prevention of malaria in young children sub-Saharan Africa.
Early clinical development was done in collaboration with WRAIR

ORIGINAL ARTICLE

Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease

S.R.S. Hadinegoro, J.L. Arredondo-García, M.R. Capeding, C. Deseda, T. Chotpitayasunondh, R. Dietze, I.I. Hj Muhammad Hussain, H. Reynales, K. Limkittikul, D.M. Rivera-Medina, H.N. Tran, A. Bouckenooghe, D. Chansinghakul, M. Cortés, K. Fanouillere, R. Forrat, C. Frago, S. Gailhardou, N. Jackson, F. Noriega, E. Plennevaux, T.A. Wartel, B. Zambrano, and M. Saville, for the CYD-TDV Dengue Vaccine Working Group*

Army and Defense Health Program Task Areas

Army

- Parasitic Diseases Research
  - Anti-Parasitic Drug Development
  - Malaria Vaccine Research
- Viral Diseases
  - Flavivirus Vaccine Research
  - Lethal Virus (Hantann, Puumala) Countermeasures
- Bacterial Diseases
  - Prevention of Diarrheal Diseases
  - Rickettsial Diseases
- Vector Control
  - Identification and Control of Insect Vectors of Infectious Diseases
- Diagnostic Systems
  - Diagnostic Systems for Infectious Diseases (far forward, rapid & easy to use point-of-care tests)

DHP

- Antimicrobial Countermeasures
- Wound Infection Prevention and Management (applied & translational product development)
- Diagnostic Systems for Infectious Diseases (integrated platform with multiple ID panels at role 3 and higher)
- Acute Respiratory Diseases/Emerging Infectious Diseases
- Military HIV Research Program*
- Combatting Antimicrobial Resistance Pgm*
- Deployed Warfighter Pgm*

*DHP Named Programs under JPC2

Strategic Science & Technology Research Gaps

- Hantann/Puumala Virus DNA Vaccine – Co-Development Partner
  - A Phase 2a Randomized, Double-Blind, Dose-Optimizing Study to Evaluate the Immunogenicity of Hantaan/Puumala Virus DNA Vaccine Administered to Healthy Adult Volunteers Using the TDS-IM Electroporation Delivery Device for Prevention of Hemorrhagic Fever With Renal Syndrome
- Detect, prevent, and manage combat wound infections and biofilm formation – Focus on IND enabling studies
  - Emphasis on Multi-Drug Resistant Organisms (MDROs) and invasive fungi/molds
  - Novel countermeasures and innovative treatment approaches – chelators, antibody therapy, phage, anti-microbial peptides, quorum-sensing inhibitors, host immunomodulation/immunotherapies, etc.
  - New chemical chemotypes/classes and biologics – antibiotics? vaccines?
- Novel drug delivery technologies for treatment/prevention of infectious disease
  - Sustained release or reduce toxicity
  - Passive prophylaxis – eliminate individual compliance issues with an emphasis on anti-malarials
- Broad spectrum antiviral drugs
  - Agents that are clinically effective for treating multiple viral families, including the potential for "designer" applications that would allow for selection of combinations of agents based on geographic deployment.

Strategic Gaps in the Pharmaceutical Systems PMO ID Portfolio

- Treatment for Cutaneous Leishmaniasis (CL) in development
  - Topical (skin) treatment for uncomplicated CL
  - 2 pivotal, Phase 3 studies complete (Tunisia and Panama)
  - Product down-select anticipated in April 2016
  - Gap: Long-term commercial/co-development partner and final product manufacturer not yet identified

Working with MIDRP

- New Product Ideas Website - http://mrmc-npi.amedd.army.mil/

- Broad Agency Announcement - http://www.grants.gov
  - On the Grants.gov homepage, click the tab "SEARCH GRANTS";
  - In the "Funding Opp #" block, enter W81XWH-16-R-BAA1

- Peer Reviewed Medical Research Program http://cdmrp.army.mil/prmrp/
  - $278.7 million in FY16
  - 39 topic areas including: Emerging Infectious Diseases, Malaria, and Vaccine Development for Infectious Diseases

Military Operational Medicine Research Program Overview

LCDR Christopher Steele, PhD
Deputy Director, MOMRP
US Army Medical Research and Materiel Command
19 April 2016

Military Operational Medicine Panel Members

LCDR Christopher Steele – Science & Technology

Deputy Director, MOMRP

Mr. Steve Hawbecker – Advanced Development

Project Manager, Medical Support Systems

US Army Medical Materiel Development Activity

Overview of MOMRP

MOMRP is an extremely diverse program

- ~90% of MOMRP projects are linked to knowledge products that are central to the DoD Total Force Fitness (TFF) and Army Human Dimension concepts.
- Supports performance sustainment, health protection and operational readiness of the Joint Warfighter across the Range of Military Operations and Service member life-cycle
- R&D to understand novel mechanisms and develop focused solutions at the group and individual level for Precision Operational Medicine

MOMRP Mission & Focus Areas

Develop effective medical countermeasures against operational stressors and prevent physical and psychological injuries during training and operations in order to maximize the health, performance and fitness of Service members and their Families.

Science

ENVIRO
Environmental Health and Protection

THREATS

- Heat/Humidity
- Cold Stress
- Altitude/Hypoxia
- Toxicants
- Dust and Air Pollution
- Inadequate Protective Equipment/ Clothing

INJURY
Injury Prevention and Reduction

THREATS

- Musculoskeletal Injury
- Blast Overpressure
- Blunt Head & Body Trauma
- Mild Traumatic Brain Injury
- Face/Eye/Spinal Injury
- Acoustic Trauma
- Laser Eye Injury

PHYSIO
Physiological Health and Performance

THREATS

- Disaggregated/Continuous Operations
- Sleep Deficit and Circadian Desynchrony
- Sustained Fatiguing Work (Physical/Mental)
- Malnutrition
- Dietary Supplement Misuse

PSYCH
Psychological Health and Resilience

THREATS

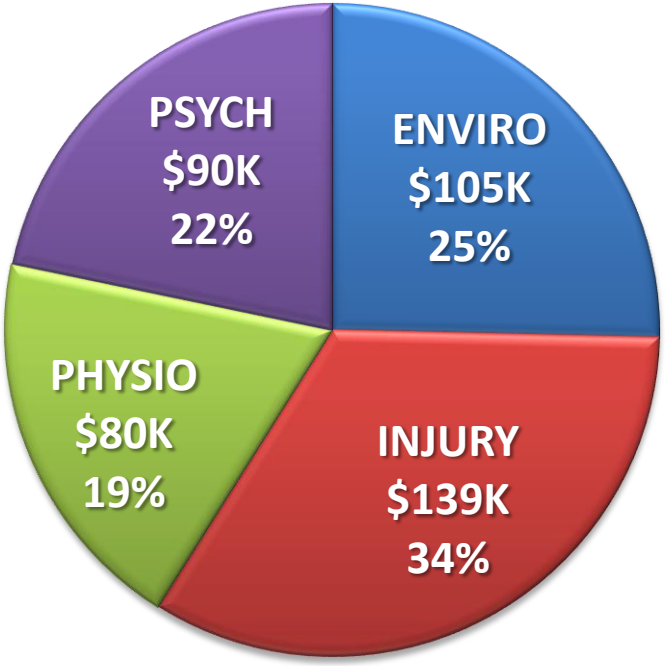
- PTSD/Other Anxiety Disorders
- Suicide Behavior
- Alcohol/Other Drug Use
- Co-occurring Mental Disorders
- Access/Retention in Behavioral Health Care
- Family Transitions and Well-being

Service Member

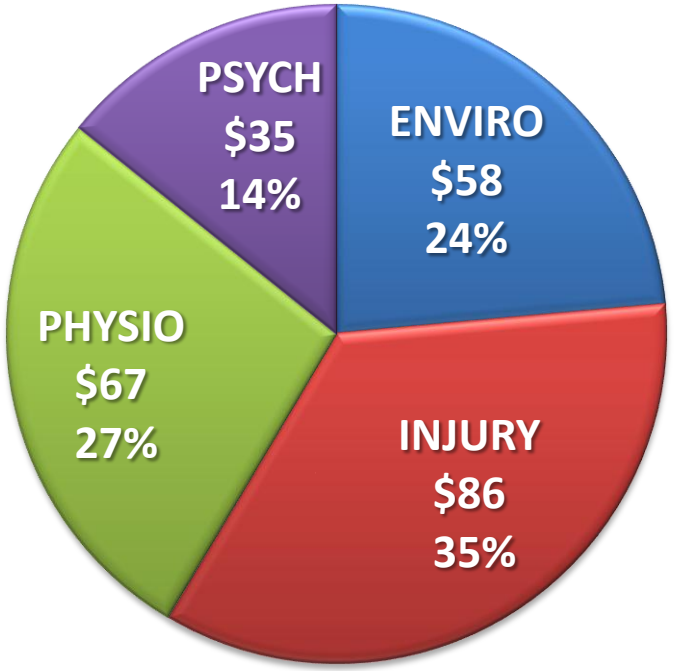
MOMRP Funding Distribution

MOMRP ARMY/DHP Total Program Distribution (FY17-23)

Army Program Tasks ($414M)

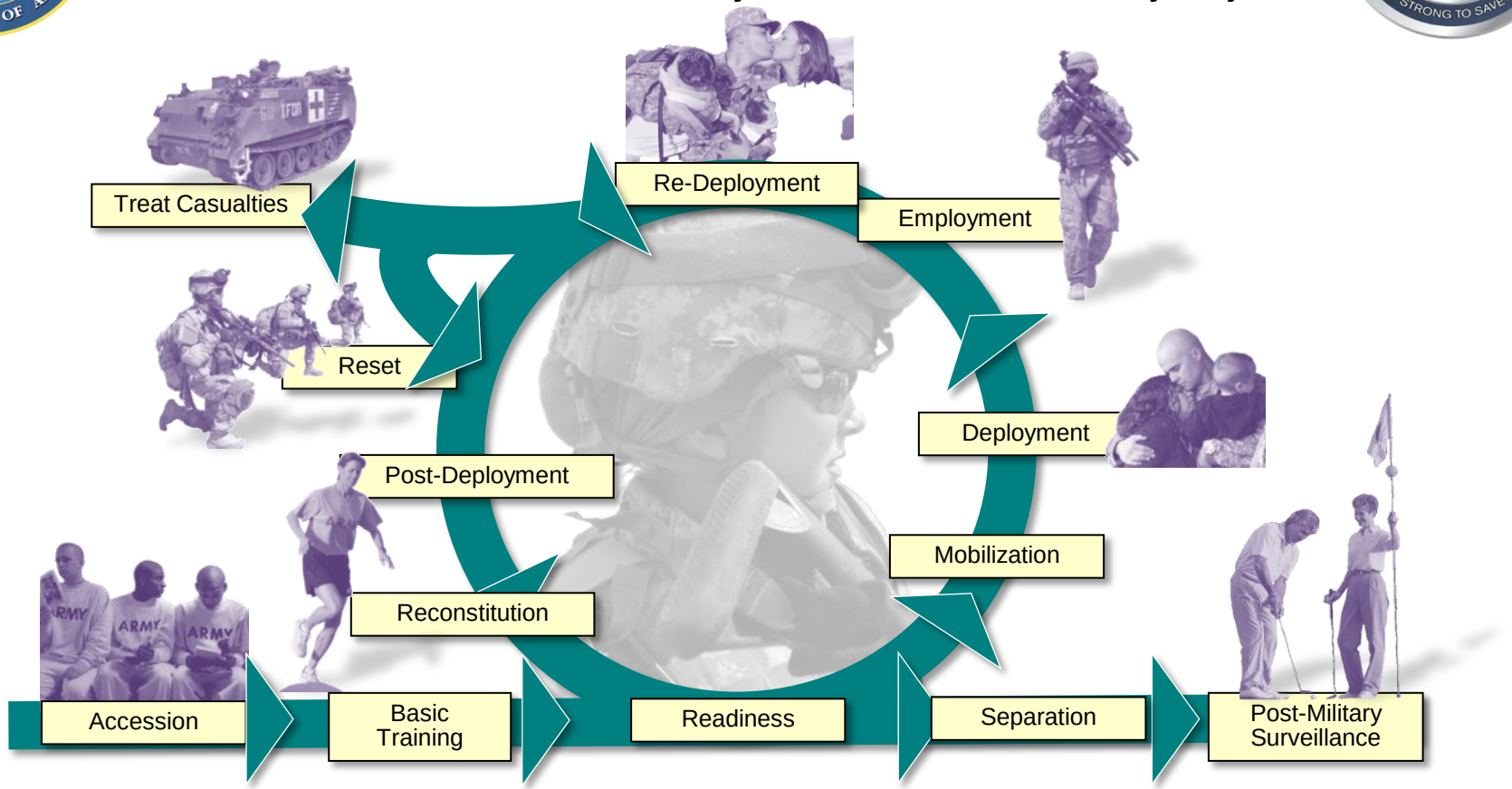


DHP (JPC-5) Program Tasks ($246M)



MOMRP Solutions Across the Lifecycle

MOMRP research touches every Service member, every day.



DEVELOPING AND MAINTAINING A FIT AND READY FORCE

- Influencing Policy, Leadership, and Training & Education
- Knowledge Products: Regulations, Standards, Guidelines, Decision Support Tools
- Materiel Products: COTS/GOTS, New Devices

MOMRP Gaps

Environmental Health & Protection (1 of 2)

Heat Exposure

- Performance and injury predictions
- Return to duty criteria following heat injury
- Microclimate cooling
- Technologies for optimal hydration status management

Altitude/Hypoxia Environments

- Performance and injury predictions
- Technologies to support sustained operations

Multi-environmental Stressors

Arctic Operations

MOMRP Gaps

Environmental Health & Protection (2 of 2)

Toxicant Exposure

- Accurate dose information for exposure to industrial chemical mixtures and material hazards
- Technologies and wearable devices to track chemical/toxic hazard exposures

Biomarker Panels to Assess SM Impact

- Toxicant environmental health hazards
- Industrial chemical mixtures found in dense urban environments

Acute and Chronic Health Effects Linked to Response-Biomarkers

MOMRP Gaps

Injury Prevention & Reduction (1 of 2)

Training and Operational Environments

- Improved understanding of the physiological mechanisms underlying musculoskeletal injuries
  - Advanced technologies for real-time assessments outside of the clinic
- Physical fitness training strategies to reduce the risk of injury from load, jolt, vibration, etc.
- Countermeasures to mitigate injury risk potential for exploitation in training environments

MOMRP Gaps

Injury Prevention & Reduction (2 of 2)

Training and Operational Environments

- Development of injury criteria for Personal Protection Equipment against blunt, blast and ballistic trauma threats
- Injury criteria and medical performance standards to protect against hearing loss, vestibular injury, and ocular facial injury
- Standards and criteria to identify when Warfighters are capable to Return-to-Duty (RTD), fully able to perform demanding tasks

MOMRP Gaps

Physiological Health & Performance (1 of 3)

Fatigue Mechanisms and Countermeasures

- Novel mechanisms in understanding/manipulating sleep for performance and health
- Sleep quality assessment that is objective but not necessarily tied to actigraphy/polysomnography – *What are we currently measuring and what are we currently missing?*
- Non-pharmacological manipulation of alertness and sleep
- Use of VALIDATED wearables for Sleep as an indicator/predictor of performance, safety and health
- Management of Circadian rhythms

MOMRP Gaps

Physiological Health & Performance (2 of 3)

Nutrition Solutions, Countermeasures and Strategies

- Nutrition solutions to optimize recovery and sustain the Joint Warfighter under extreme conditions
- Nutritional interventions for mission reset and injury recovery -- countermeasures for physical and cognitive degradation following military operations
- Protection strategies to mitigate operational stress
- Tailored, modular ration components to improve readiness

MOMRP Gaps

Physiological Health & Performance (3 of 3)

Physiological Basis of Resilience and Cognitive Readiness

- *Sustain robust cognitive function* in Service members under acute operational psychological/physiological stressors
- *Promote adaptability to novel, militarily-relevant demands* and improve cognitive function in Service members over the course of a training cycle or career

MOMRP Gaps

Psychological Health & Resilience (1 of 2)

Service Member Resilience

- Evidence-based individual and group interventions and technologies to promote Resilience
- Resilience training that incorporates key behavioral health outcomes
- Biomarkers of resilience

Behavioral Health

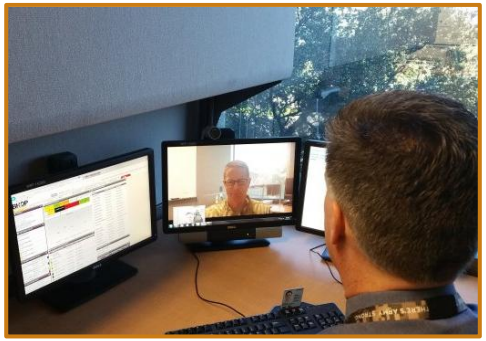
- Tools and technologies to better prevent, diagnose, and treat mental health issues such as suicide and substance abuse

MOMRP Gaps

Psychological Health & Resilience (2 of 2)

Psychological and Behavioral Health

- Non-self report assessment technologies of psychological well-being and status
- Telemedicine and mental/behavioral health approaches that overcome barriers/challenges
- Identification/validation of biomarkers for Post Traumatic Stress Disorder (PTSD)
- Translational efforts on the diagnosis and treatment of PTSD



Interagency Psych Health Collaborations

- National Research Action Plan (NRAP) to coordinate psychological health research across DoD, VA and NIH (NIMH/NIDA/NIAAA
- Army Study to Assess Risk and Resilience in Service Members (Army STARRS and STARRS-Longitudinal Study (STARRS-LS))
- Consortium to Alleviate PTSD (CAP)
- Joint review and analyses of integrated psychological health research programs across DoD, VA and NIH (NIMH/NIDA/NIAAA)
- FY13 Joint Program Announcement, “Substance Abuse Prevention and Health Promotion”, with NIDA/NIAAA/NCCAM

Every Service Member, Every Day

Advanced Development

RESEARCH → ADVANCED DEVELOPMENT → FIELDED PRODUCT

- Prototyping (Durability/Packaging)
- Manufacturing Evaluation
- Validation and Verification
- Logistics Analysis/Planning
- Integration with User Representatives
- User Evaluation
- Transition/integration to other PEOs/Services

DoD 5000

Materiel Solution Analysis → *Technology Maturation and Risk Reduction* → *Engineering and Manufacturing Development* → *Deployment* → *Operations and Sustainment*

Bridging the Valley of Death

Questions?

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