ANTIBIOTIC RESISTANCE AND WOUND INFECTIONS

WRAIR PROTECTS YOUR SIX

Protecting your brain - the most important six inches on the battlefield

CENTER FOR MILITARY PSYCHIATRY AND NEUROSCIENCE

- Blast Induced Neurotrauma and Neuroprotection
- Sleep & Resilience
- Team Performance and Mental Fitness
- Military Psychiatry

Protecting the most important six microns between you and the threat of disease

CENTER FOR INFECTIOUS DISEASE RESEARCH

- Vaccines & Entomology
- Viral & Bacterial Diseases
- Military HIV Research Program
- Experimental Therapeutics & Emerging Infectious Diseases

WHETHER YOU'RE AT HOME STATION OR SIX THOUSAND MILES AWAY

WALTER REED ARMY INSTITUTE OF RESEARCH'S MISSION

Discover, design, and develop solutions for military relevant infectious disease and brain health threats through innovative research protecting and optimizing warfighter lethality.

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PROMOTED HASHTAGS

#WRAIRProtectsYourSix
#DefeatInfections #WorldHealth
#MaximizeHumanPotential
#ForgeTheFuture #SoldierHealth

WALTER REED ARMY INSTITUTE OF RESEARCH IS A SUBORDINATE COMMAND OF MRDC

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DEFEATING WOUND INFECTIONS

THE "GOLDEN HOUR" LIMITED WOUND INFECTIONS

WORLD WAR II

Avg. Evacuation Time: >24 hrs

Wounded in Action: 671,000

Rate of Infected Wound: 25% - 30%

VIETNAM

Avg. Evacuation Time: 4- 12hrs

Wounded in Action: 304,000

Rate of Infected Wound: 4% - 27%

OEF/OIF

Avg. Evacuation Time: 45 to 90 min

Wounded in Action: 52,000

Rate of Infected Wound: 9% - 18%

DELAYED CARE IN THE "GOLDEN DAY+" MAY INCREASE WOUND INFECTIONS THROUGH:

EVACUATIONS

During near-peer competition, the time frame for evacuations may increase beyond the **golden hour**.

RESUPPLY

In the absence of air superiority, resupply for medical materiel may be greatly delayed.

TREATMENT

With late evacuations and challenges in resupply we predict treatment will go from the **golden hour** to the **golden day+**, resulting in delayed wound care.

WHAT WE'RE DOING ABOUT IT

WRAIR is developing new, far-forward preventive and therapeutic interventions that extend the **golden hour** to the **golden day+**, which is required to sustain a lethal and responsive force during large-scale combat operations.

Framing the Problem

State-of-the-Art Analysis

Our proactive, worldwide surveillance allows us to know what threats exist in the deployed environment. This enables us to understand in real-time what is there and how superbugs adapt to antibiotics so we can then inform in-theater medical personnel.

Multi-drug Resistant (MDR) Bacteria Repository

WRAIR's Multidrug-Resistant Organism Repository & Surveillance Network currently houses a repository of over 70,000 MDR bacteria. These bacteria represent the genetic breadth observed in military treatment facilities and are used to develop new antibiotics.

Wound Infection Solutions

Bacteriophage Therapeutics

We leverage bacteriophages, (viruses that kill bacteria), to develop novel solutions for antibiotic-resistant superbugs.

Structure-Based Drug Design

We use structure-based drug design to develop new antibiotic solutions.

Monoclonal Antibodies and Vaccines

We leverage the power of our own immune systems to develop immune-based solutions for bacterial infections.

Pathophysiology of Infection

Understanding the mechanics of infection leads to better prediction, prevention, and treatment.

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SUPERBUGS

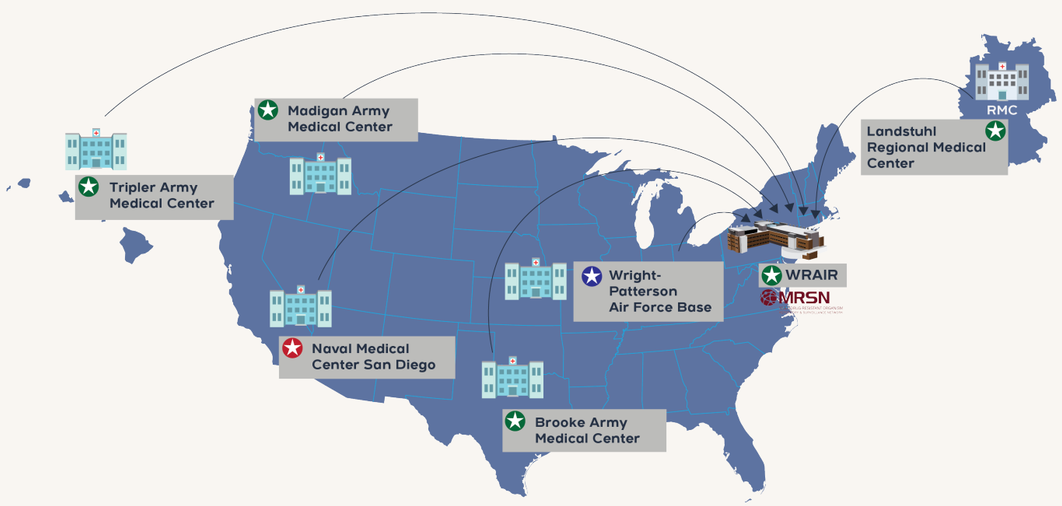
WHAT'S THERE AND HOW DO WE PREVENT IT.

WRAIR's Multidrug-Resistant Organism Repository & Surveillance Network (MRSN), established in 2009, is the sole entity within the DOD engaged in real-time surveillance of multidrug-resistant (MDR) bacteria, superbugs, and molecular outbreak investigation assistance across the entire Military Healthcare System (MHS) with surveillance efforts across all geographic combatant commands.

Military Relevance

- The 2019 U.S. Military Infectious Diseases Threat Prioritization Panel named MDR bacteria as one of the highest tier 1 infectious disease threats, recognizing the high operational risk associated with these pathogens.
- As the U.S. military executes its missions worldwide, health care providers in military medical treatment facilities (MTFs) are faced with the dilemma of how to treat infections caused by MDR bacteria, a challenge made worse in operational environments.

1 DISEASE OUTBREAKS IN THE MILITARY HEALTHCARE SYSTEM



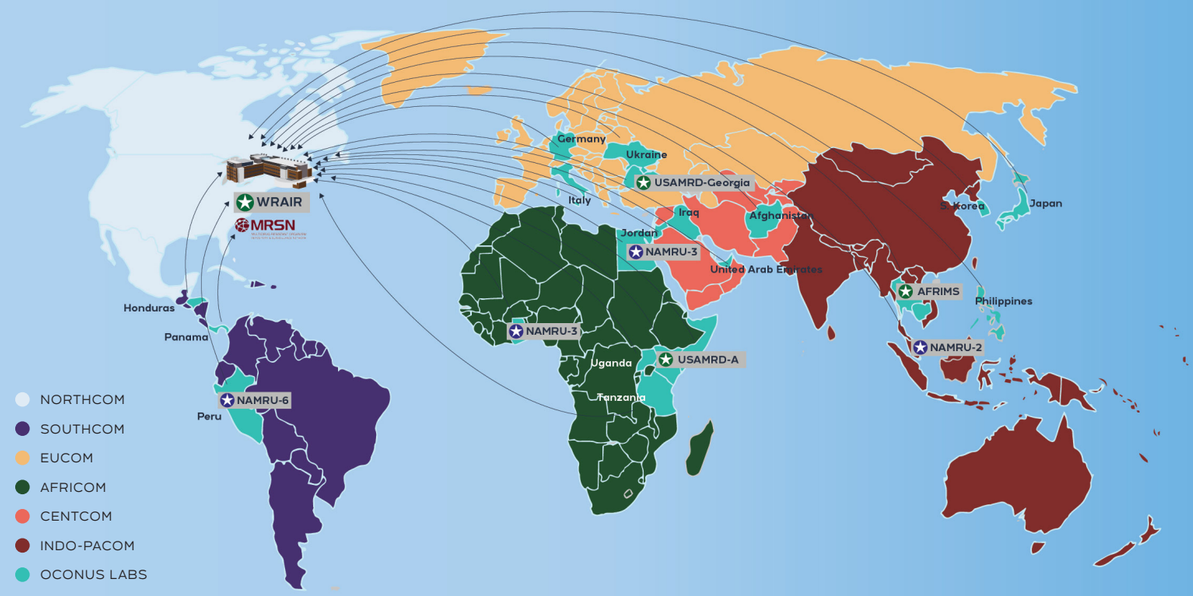
DISEASE OUTBREAK INVESTIGATIONS IN THE MHS

- Response assistance requested by healthcare professionals
- 6-8 outbreak investigations per month
- Turnaround time as short as 48-72 hours

MTF MDR ORGANISMS SURVEILLANCE

- All MTFs send MDR bacteria to MRSN in accordance with DOD/DHA policy
- 500-800 bacterial samples per month received from around the world
- MRSN performs real-time molecular epidemiology

2 GLOBAL ANTIBIOTIC RESISTANCE SURVEILLANCE

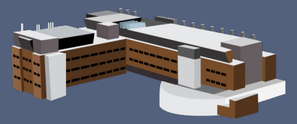


GLOBAL ANTIBIOTIC RESISTANCE SURVEILLANCE

- OCONUS and Global Emerging Infections Surveillance (GEIS) funded labs in 22 countries
- Thousands of bacteria collected per year
- Track superbugs worldwide
- Provide actionable infectious disease surveillance data to geographic combatant commands

COMBATING ANTIBIOTIC-RESISTANT BACTERIA (CARB)

- Presidential Executive Order 13676, established Combating Antibiotic-Resistant Bacteria (CARB) in 2015 to identify new antibiotics for use against MDR bacteria of military and public health importance.
- WRAIR was tasked with other governmental organizations to transition new antibiotic drug candidates to advanced development due to its rich history in drug discovery and development.



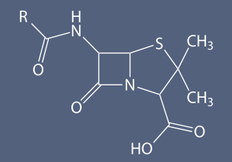
WRAIR'S CAPABILITY

WRAIR has leveraged internal capabilities between Experimental Therapeutics, the MRSN, and Wound Infections Department to enable a military-relevant antibiotic drug discovery program.

THIS CAPABILITY CAPITALIZES ON

>800K unique drug-like compound library

- access to **>70K** clinical bacterial isolates
- *in vitro* and *in vivo* pre-clinical models
- automation to enable high-throughput, low-cost screening of drug candidates



>50,000 COMPOUNDS
selected for advance anaylsis

>4,500 COMPOUNDS
screened per week

NEW SOLUTIONS FOR COMBAT-RELATED WOUND INFECTIONS

DELAYED CARE IN THE GOLDEN DAY+ MAY INCREASE WOUND INFECTIONS

The majority of infections in military and civilian hospitals are caused by MDR ESKAPE-E pathogens.

- ESKAPE-E pathogens are found everywhere we send Service Members and cause drug-resistant infections.
- New antibacterial drugs developed at WRAIR will be effective against antibiotic-resistant ESKAPE-E infections.

WHAT WE'RE DOING ABOUT IT

- Identify new targets for antibiotic and monoclonal therapeutics against ESKAPE-E pathogens.
- Leverage phage's ability to kill bacteria to make novel phage cocktails against ESKAPE-E pathogens.
- Understand unique physiology of combat trauma infections to improve clinical guidelines for prolonged field care.

1hr GOLDEN HOUR EVACUATION (OIF/OEF)

52,352[1] wounded in action

On average 45 - 90[2] minutes from injury to field hospital

49%[3] of those wounded had bacteria in their wounds

34%[4] of combat casualties develop infections during their initial hospitalization

27%[5] deep infection rate for type III open tibia fractures which may lead to unnecessary amputations

24hr How many infections will we have when we extend to the Golden Day+?

1. United States Department of Defense. OIF/OEF Casualty Status. www.defense.gov/casualty.pdf (Last accessed October 13, 2017).
2. Kotwal RS1, Howard JT2, Orman JA2, Tarpey BW2, Bailey JA3, Champion HR4, Mabry RL2, Holcomb JB5, Gross KR3. The Effect of a Golden Hour Policy on the Morbidity and Mortality of Combat Casualties. JAMA Surg. 2016 Jan;151(1):15-24. doi: 10.1001/jamasurg.2015.3104.
3. MAJ Clinton K. Murray, MC USA*; MAJ Stuart A. Roop, MC USA‡; LTC(P) Duane R. Hospenthal, MC USA*; COL David P. Dooley, MC USA*; CPT Kimberly Wenner, MC USA‡; MAJ John Hammock, MC USA‡; CPT Neil Taufen, MC USA‡; MAJ Emmett Gourdine, MS USA Bacteriology of War Wounds at the Time of Injury. MILITARY MEDICINE, 171, 9:826, 2006
4. Weintrob AC1,2,3, Murray CK4, Xu J5, Krauss M5, Bradley W1,2, Warkentien TE3, Lloyd BA6, Tribble DR1. Early Infections Complicating the Care of Combat Casualties from Iraq and Afghanistan. Surg Infect (Larchmt). 2018 Apr;19(3):286-297. doi: 10.1089/sur.2017.240. Epub 2018 Jan 19.
5. Travis C. Burns, MD, Daniel J. Stinner, MD, Andrew W. Mack, MD, Benjamin K. Potter, MD, Rob Beer, MD, Tobin T. Eckel, MD, Daniel R. Possley, DO, Michael J. Beltran, MD, Roman A. Hayda, MD, Romney C. Andersen, MD, John J. Keeling, MD, Harold M. Frisch, MD, Clinton K. Murray, MD, Joseph C. Wenke, PhD, James R. Ficke, MD, Joseph R. Hsu, MD, and the Skeletal Trauma Research Consortium, Fort Sam Houston, Texas Microbiology and injury characteristics in severe open tibia fractures from combat, J Trauma Volume 72, Number 4

NEW ANTIBIOTICS BY STRUCTURE-BASED DRUG DESIGN

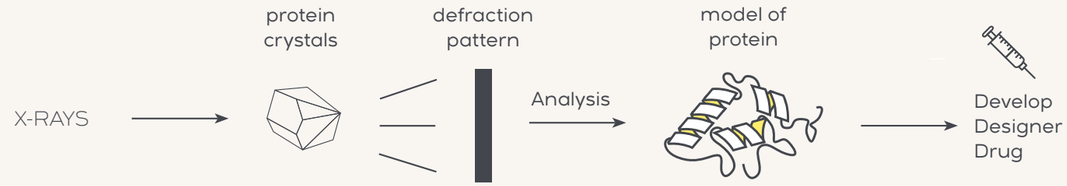
- WRAIR is the home of the Army's only center for x-ray crystallography for antibiotic discovery.
- The center combines virtual chemical library screening, protein structure, medicinal chemistry and pre-clinical models to discover and develop novel therapeutics to address the problem of multidrug-resistant (MDR) bacteria.
- The advantage of this approach is that designed drugs are highly specific to target with minimal toxicity to patients.

ESKAPE-E

- **E**NTEROCOCCUS FAECIUM
- **S**TAPHYLOCOCCUS AUREUS
- **K**LEBSIELLA PNEUMONIAE
- **A**CINETOBACTER BAUMANNII
- **P**SEUDOMONAS AERUGINOSA
- **E**NTEROBACTER SPECIES
- **E**SCHERICHIA COLI

Structure-Based Drug Design

Our state-of-the-art x-ray crystallization allows us to better design countermeasures.



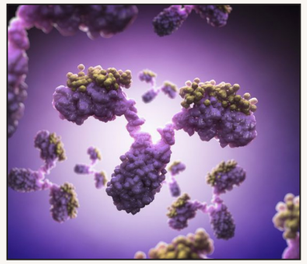
Success Story

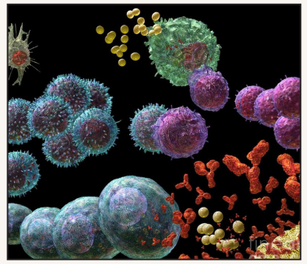
A. baumannii OmpW2 protein (Lock) target on bacteria

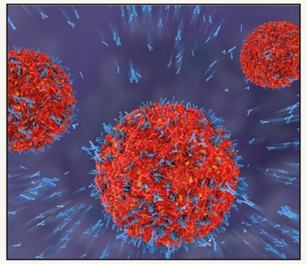
Drug (Key) design antibiotics

WRAIR has developed and is optimizing effective inhibitors against *A. baumannii* & *K. pneumoniae*, two gram-negative bacteria that were often isolated during OIF/OEF. Wound infections by these organisms are often highly resistant to most antibiotics.

MONOCLONAL ANTIBODIES AND VACCINES







Antibodies can:

inactivate bacterial toxins

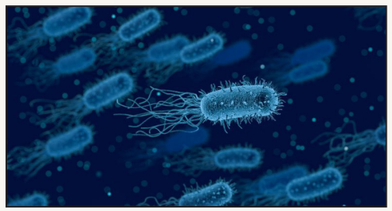
activate the immune system

destroy bacteria

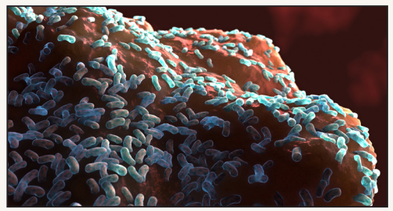
- Antibodies are proteins that provide immunity.
- WRAIR investigators have successfully identified protein targets on MDR ESKAPE-E organisms suitable for antibody-based therapy.
- Our analysis suggests that pre-treatment with monoclonal antibodies may prevent infections *in vivo*.

A PROMISING NEW APPROACH *Acinetobacter baumannii*

- Vaccines are durable and effective biologics to prevent infection and enhance Soldier durability.
- A combination of radiation-killed *A. baumannii* grown in suspension and biofilm protects from MDR *A. baumannii* infection in preclinical models over 90% of the time.



Bacteria growing in suspension express specific proteins



Bacteria growing as biofilms express different proteins

Combining bacteria growing under different conditions and preservation enables the designing of better vaccines

BACTERIOPHAGE THERAPEUTICS

- WRAIR develops bacteriophage therapeutics against superbug MDR bacteria.
- Phages are viruses that selectively kill bacteria; we are selecting and developing phage cocktails for MDR bacteria as new therapeutics for people.

1919:
Félix d'Hérelle successfully implemented phage therapy.

1930:
Before antibiotics, Eli Lilly Company manufactured phage for infections.

2019:
WRAIR formulated and vialed the Army's phage cocktail for therapeutic use.

WHAT IS A PHAGE COCKTAIL?

1. **Find phage**

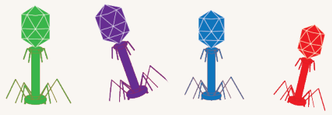
Environment

And /Or

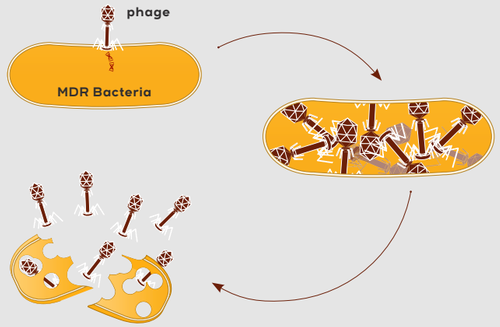
Sewage Treatment Facility

2. **Analyze & describe phage activity**

3. **Create phage cocktail**



each phage is different



1. Phage invades target cell
2. Phage reproduces within target cell
3. Phage bursts from target cell, destroying it and begins search for new target cell

SUCCESS STORY

- WRAIR investigators have successfully compiled panels of potent phages to treat 75-100% MDR ESKAPE-E organisms collected from across the globe.
- *P. aeruginosa* phage cocktail was active against 88% of MRSN's MDR isolates from our MDR repository.
- WRAIR produced the first durable fixed cocktail vialed by the Pilot Bioproduction Facility in the fall of 2019.

FORGING THE FUTURE

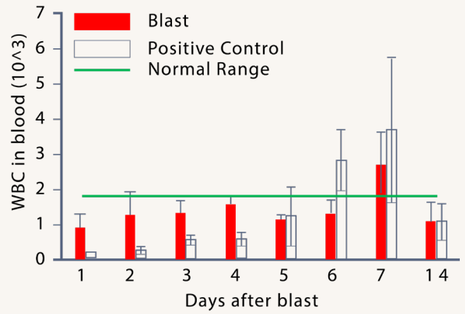
- Formulate a 5-15 phage cocktail products for ESKAPE-E infection treatment.
- Evaluate *P. aeruginosa* cocktail as well as fixed therapeutic phage cocktails against *Enterobacter cloacae* and *Escherichia coli* in Phase I-II clinical trials.
- Expand capability to include phage engineering and phage adaptation/training for potent durable cocktails for far-forward deployment.

PATHOPHYSIOLOGY OF INFECTION

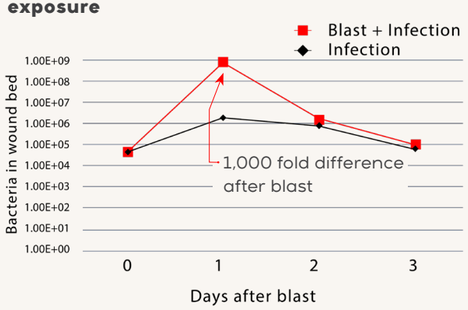
WOUND INFECTIONS MAY BE THE HALLMARK OF MULTI-DOMAIN OPERATIONS

WRAIR has developed pre-clinical models involving complex polytrauma and infection to understand how wound contamination turns into infection. WRAIR has developed a combat trauma model involving blast to better simulate battlefield-like wounds:

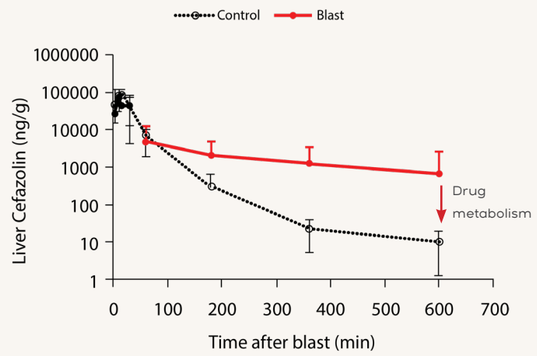
- **White blood cell count suppressed after blast exposure**



- **More bacteria are found in wound after blast exposure**



- **Blast alters antibiotics metabolism leading to potential complications and inefficacy**



COMBAT TRAUMA ALTERS HUMAN PHYSIOLOGY AND PREDISPOSES THE BODY TO INFECTIONS BY:

- Disrupting the first line of defense, your skin
- Introducing mono- or poly-microbial contamination infection
- Causing hemorrhage leading to resuscitation

WHAT WE'RE DOING ABOUT IT

- Continue to decipher the intricate relationship between combat polytrauma, infections and sepsis for data-driven clinical practice guideline revisions and field medicine.
- Assess the effects of resuscitation fluids and antibiotics dosing schedule on infection outcomes.
- Leverage polytrauma of infection pre-clinical models to evaluate emerging solutions and therapuetics.

FORGING THE FUTURE

LAYERED DEFENSE FOR DURABLE SOLDIERS

1. Appropriate drugs for unique complex polytrauma injuries.
2. Understanding unique phyisology after devestating traumatic injury and finding drugs that work in this setting.
3. Assess new emerging materiel solutions to prevent infections.

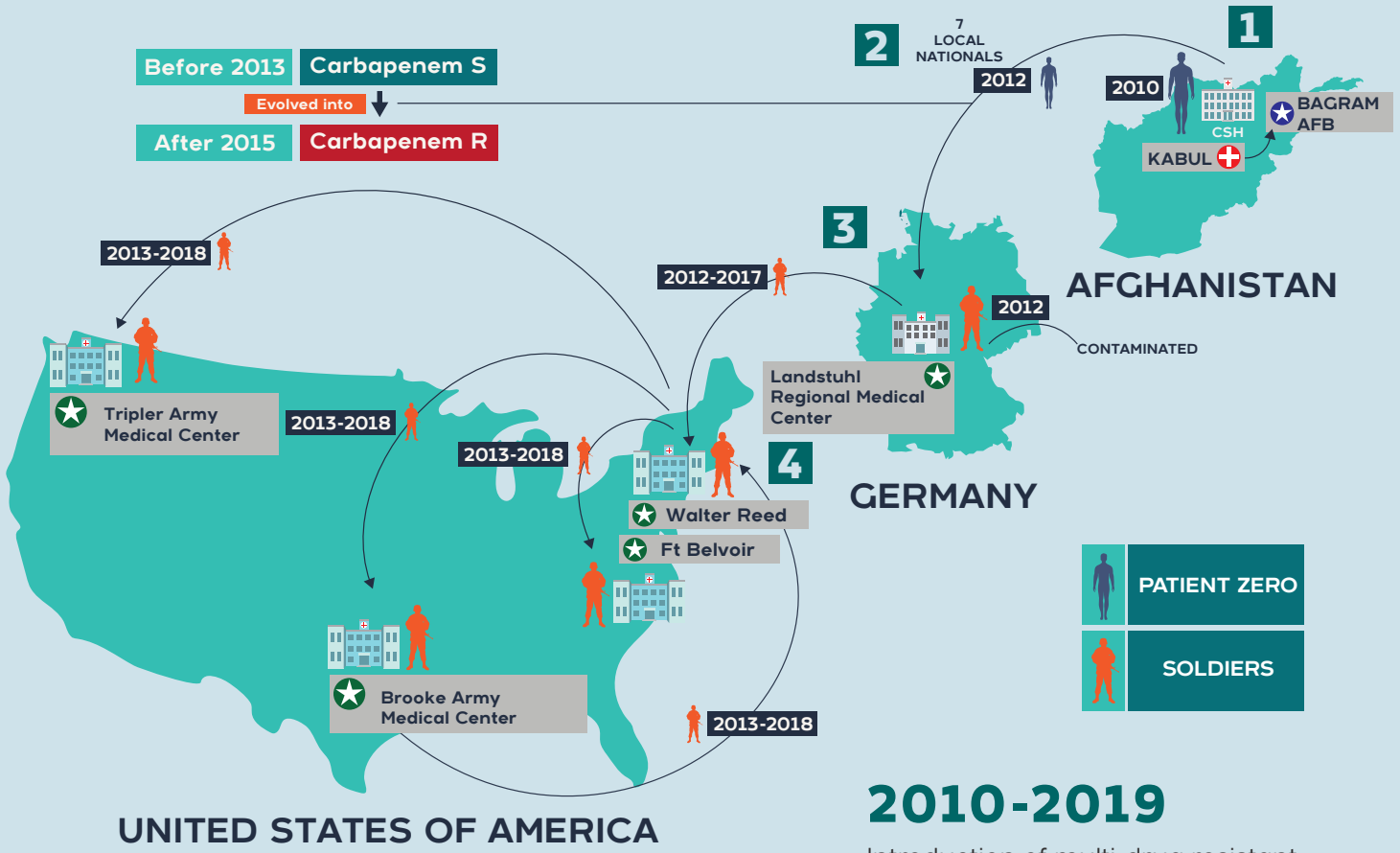
KEY PARTNERSHIPS

Our robust partnerships provide a competitive advantage and fortify our strategic depth to deliver solutions for all phases of multi-domain operations. Partnerships with biotech and pharmaceutical companies in the development of drugs and vaccines enables cost sharing, expedites practical interim solutions, speeds up timelines and takes advantage of robust development platforms in the civilian sector.

U.S. GOVERNMENT & DEPARTMENT OF DEFENSE	· BEI-ATCC · BDRD · CCCRP · CDC	· DHA · DTRA · FDA · MIDRP	· MOMRP · NAMRU-6 · NIH · NMCPHC	· NMRC · USAISR · USUHS
ACADEMIA	· Battelle Memorial Institute · California State University · Center for Innovative Phage Applications and Therapeutics · Emory University · Indiana Univ.	· Institute Pasteur · J. Craig Venter Institute · Johns Hopkins Univ. · Katholieke Universiteit Leuven · Liberty Univ.	· Ludvig Boltzmann Institute for Experimental Traumatology · National Pirogov Memorial Medical University · Univ. of Aberdeen · Univ. at Buffalo-SUNY	· Univ. of California San Diego · Univ. of Colorado · Univ. of Grenoble Alpes · Univ. of Maryland School of Medicine · Univ. of Nebraska Medical Center	· Univ. of North Carolina at Chapel Hill · Univ. of Pittsburgh · Univ. of Texas · Washington State University
INDUSTRY	· Bacterioscan Inc. · Distributed Biologics, Inc. · Droplette Ltd. · Klox Technologies · Matoke Holdings	· MotifBio plc · NanoWorld AG · Rain Scientific Tissue · Regeneration Technoogies · Revgenex Ltd.	· Roche Ltd. · Spero Therapeutics, Inc. · VenatoRx Pharmaceuticals Inc.		
HOSPITAL	· Children's National Hospital · Baltimore VA Medical Center · Boston Children Hospital	· Landstuhl Regional Medical Center · Martinsburg VA Medical Center · MedStar	Washington Hospital Center · Rochester Regional Health · Walter Reed	National Military Medical Center Washington DC VA Medical Center	

TRACKING SUPERBUGS

Tracking the movement of MDR organsims globally is a key component of layered defense whereby the prevention and control of infectious diseases are informed by surveillance of organisms (superbugs) surrounding the warfighter.



2010-2019

Introduction of multi-drug resistant *Pseudomonas aerguinosa* from a local hospital in Afghanistan to the Military Healthcare System, via Landstuhl Regional Medical Center

LAYERED DEFENSE AGAINST MDR BACTERIA

SURVEILLANCE & STATE-OF-THE-ART ANAYLSIS

Proactive, worldwide surveillance via our CONUS, OCONUS labs

PREVENTIVE TREATMENT

Monoclonal antibodies and vaccines

DIAGNOSTICS FOR AUSTERE MEDICINE

Early warning/detection of infection

Identify biomarkers of early stages of sepsis

Enable precision medicine at point-of-injury

PRODUCTS FOR AUSTERE MEDICINE

Potent drugs with low toxicity

Stable phage cocktails

Polytrauma calibrated PK/PD profile of drugs

Multi-component gauze

Assess emerging tech

LEVERAGE FOR FUTURE SOLUTIONS

Use state-of-the-art system and repository of over 70,000 MDR samples to design new countermeasures