

THE US DEPARTMENT OF DEFENSE HEMORRHAGE AND RESUSCITATION RESEARCH AND DEVELOPMENT PROGRAM

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ABSTRACT—Data from recent conflicts demonstrate the continuing need for research and development focusing on hemorrhage control, fluid resuscitation, blood products, transfusion, and pathophysiologic responses to traumatic hemorrhage. The US Department of Defense Hemorrhage and Resuscitation Research and Development Program brings together US Department of Defense efforts and is coordinated with efforts of our other federal government, industry, international, and university-based partners. Military medical research has led to advances in both military and civilian trauma care. A sustained effort will be required to continue to advance the care of severely injured trauma patients.

KEYWORDS—Hemorrhage, Resuscitation, Department of Defense

INTRODUCTION

As in previous conflicts, over a decade of US involvement in wars in Iraq and Afghanistan has continued to pose significant challenges in the medical care of severely injured casualties and in the logistics required to deliver that care. For example, among combat casualties, hemorrhage was identified as the leading cause of potentially preventable deaths occurring before a medical treatment facility was reached. A study of battlefield fatalities occurring between October 2001 and June 2011 found that of the 4596 fatalities reviewed approximately nine of 10 occurred before reaching a surgical capability, and of those, 90% were due to hemorrhage. Further analysis suggested that up to 24% of all combat deaths could be potentially survivable with new technologies and approaches to the treatment of hemorrhage in the prehospital environment (1). There is a continuing need for improved treatments to stop bleeding and mitigate the pathophysiologic consequences to hemorrhagic shock.

In Iraq and Afghanistan, casualties with hemorrhagic shock have often received blood transfusions at forward-positioned hospitals and surgical teams. The magnitude of this requirement is evidenced by the fact that more than 330,000 U of blood products had been transfused in the combat theater as of the end of 2014 (2). Delivering blood products where needed on the battlefield presents a significant logistical challenge for the military, and best practice use of blood products will continue to be a significant part of combat casualty care for the foreseeable future.

Casualty evacuation times averaged 90 min between 2001 and 2009 and improved to less than 45 min after 2009. Current estimates are that in some future scenarios it will be necessary to manage casualties for longer periods in the field, sometimes for up to 72 h. To meet this challenge, it will be necessary to move

more capabilities forward, closer to the point of wounding and during transport, addressing the “golden hour” based on patient physiology to make treatment less dependent on rapid evacuation to a physical facility (3). This change in paradigm will generate the need for improved en route care and for development of next-generation approaches to hemorrhage control and resuscitation.

These challenges highlight the importance of military-oriented medical research that is driven by requirements, or capability gaps, and aimed at reducing morbidity and mortality from injuries sustained in combat (4, 5). The Hemorrhage and Resuscitation Research and Development Program, as a component of the Combat Casualty Care Research Program, includes the US Department of Defense (DoD) efforts in the general areas of hemorrhage control, fluid resuscitation, blood products, transfusion, and pathophysiologic responses to traumatic hemorrhage, with efforts ranging from basic and discovery research through clinical development. The purpose is to provide improved methods, drugs, and devices to stop life-threatening bleeding; restore lost blood volume; and mitigate the consequences of hemorrhage.

The program is focused on 4 strategic objectives. The initial, rapid control of severe bleeding at or near the point of injury is of primary importance and is required to enable all subsequent resuscitative procedures. Therefore, the first strategic objective is to provide technologies to control bleeding in the prehospital environment. As mentioned, battlefield transfusion will continue to be an essential part of combat casualty care. This is recognized in the second strategic objective, to provide safer, more effective, and more logistically supportable blood products. It is understood that the development of individual, new technologies is not sufficient to optimally advance casualty survivability. We must understand how best to apply new technologies, alone or in combination. For this reason, the third strategic objective is to provide technologies and knowledge sets for improved damage control resuscitation. Future combat scenarios are expected to involve prolonged field care, with evacuation times up to 72 h before surgical care. Next-generation approaches to resuscitation will be required. Therefore, the fourth strategic objective is to provide next-generation resuscitation for prolonged prehospital management and casualty survivability.

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TABLE 1. DoD hemorrhage and resuscitation lines of effort

Line of effort	Goal
Improved blood products	Develop safer and more logistically supportable blood products for transfusion
Damage control resuscitation	Identify the best ways to use existing and newly developed blood products, drugs, and fluids
Coagulopathy of trauma	Elucidate mechanisms to identify diagnostic and therapeutic targets for the development of rapid diagnostics and therapeutics to prevent or treat coagulopathy of trauma
Immune/inflammatory modulation	Evaluate promising approaches and identify key mechanisms leading to the long-term ability to modulate inflammatory responses of the patient
Metabolic and tissue stabilization	Evaluate promising approaches and identify key mechanisms leading to the long-term ability to modulate/stabilize metabolic responses (including oxygen delivery)
Hemostatics	Evaluate/identify existing products and develop new products or procedures to control bleeding

The end state, which we hope to achieve by 2025 to 2030, will be that potentially survivable casualties will no longer be limited by technology shortfalls related to hemorrhage.

To achieve these strategic objectives, the program is executed across 6 lines of effort or thrust areas of research (Table 1). Although these areas are interrelated, each represents a distinct, focused, and sustained effort with near mid- and long-term objectives. As shown in Figure 1, the DoD's current development pipeline for hemorrhage and resuscitation includes products or programs addressing each of our lines of effort, at various stages of research and development. The program includes not only discovery science and product development, but also significant clinical trials addressing topics with potential to influence clinical practice. Following US Food and Drug Administration approval, products often must undergo additional test and evaluation before full fielding, such as in the case of junctional and abdominal tourniquets that have recently become available.

Importantly, DoD research and development is not done in isolation. A significant portion of the program is integrated as

a part of interagency collaborations involving other parts of the US Government, including the Biomedical Advanced Research and Development Authority, the National Heart Lung and Blood Institute, and the US Food and Drug Administration Office of Counterterrorism and Emerging Threats (6). There are also significant collaborations with other DoD research and development programs, such as forward surgical and intensive critical care, en route care, and neurotrauma. We also communicate and coordinate with our military allies.

The research programs are executed by intramural DoD laboratories and other government organizations, by our industry partners, and by independent, academically based researchers. While DoD laboratories provide a unique and vital capability, extramural investigators are a very important part of the program. Each year, there are several announcements sponsored by the Army, Navy, Air Force, Defense Health Agency, the Defense Advanced Research Projects Agency, and the US Special Operations Command requesting research or technologies to meet DoD requirements. In addition, Congress may request research topics through the Congressionally

Hemorrhage and Resuscitation Development Pipeline – Current Snapshot of Functional R&D Stages

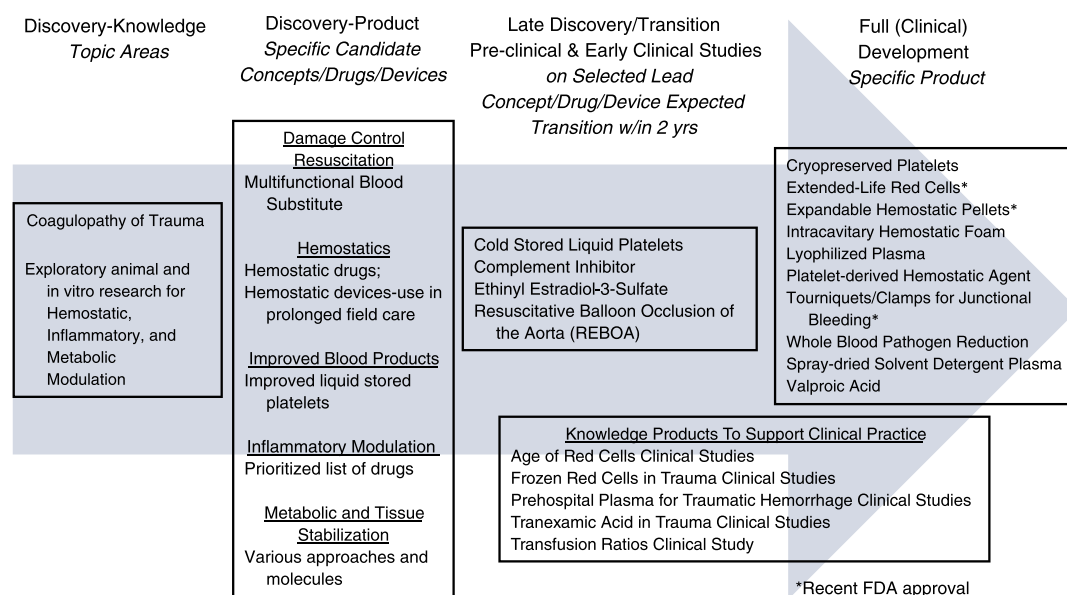


FIG. 1. The US Department of Defense Hemorrhage and Resuscitation Research and Development pipeline.

Directed Medical Research Program. Most can be found at www.grants.gov, www.dodsbir.net, and www.fbo.gov.

In recent years, military medical research has led to a reduction in the case fatality rate for combat trauma (5). Advances have contributed to the improved survival and recovery of US service personnel and have also benefited civilian trauma practice (4, 5, 7, 8). Recent advances have included the development of advanced topical hemostatics and limb tourniquets, guidelines for 1:1 (plasma to red cells) transfusion ratios for severe trauma, and devices to control junctional and other difficult to compress bleeding, among others (9). Within the next several years, it is expected that the program will deliver US Food and Drug Administration–approved dried plasma, extended shelf-life platelets, pathogen reduction technology for whole blood, devices for intracavitary bleeding, and new information on how best to use products such as tranexamic acid and plasma in the prehospital environment (10). In the longer term, the DoD hopes to develop specific diagnostics and therapeutics for the acute coagulopathy of trauma and drugs to modulate metabolic and inflammatory processes to prolong casualty survivability.

Significant progress has been made, but there is much more to do. Continued progress will require a deliberate and sustained investment to benefit both the military and civilian communities, where in the field of trauma there is little dedicated research funding by other federal agencies (5).

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