Introduction to DARPA and FSHARP Program

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DARPA's Mission: Breakthrough Technologies for National Security


Department of Defense Directive

1958: DARPA Founded

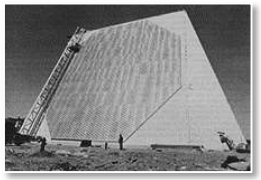
1963: Arecibo Observatory

1977: Stealth Technology

1988: UAVs

2004: Autonomous Vehicle Grand Challenge

2014: mRNA Vaccine



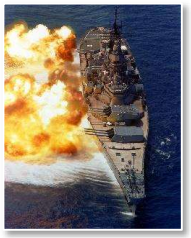
1959: Phased Array RADAR

1969: ARPANET

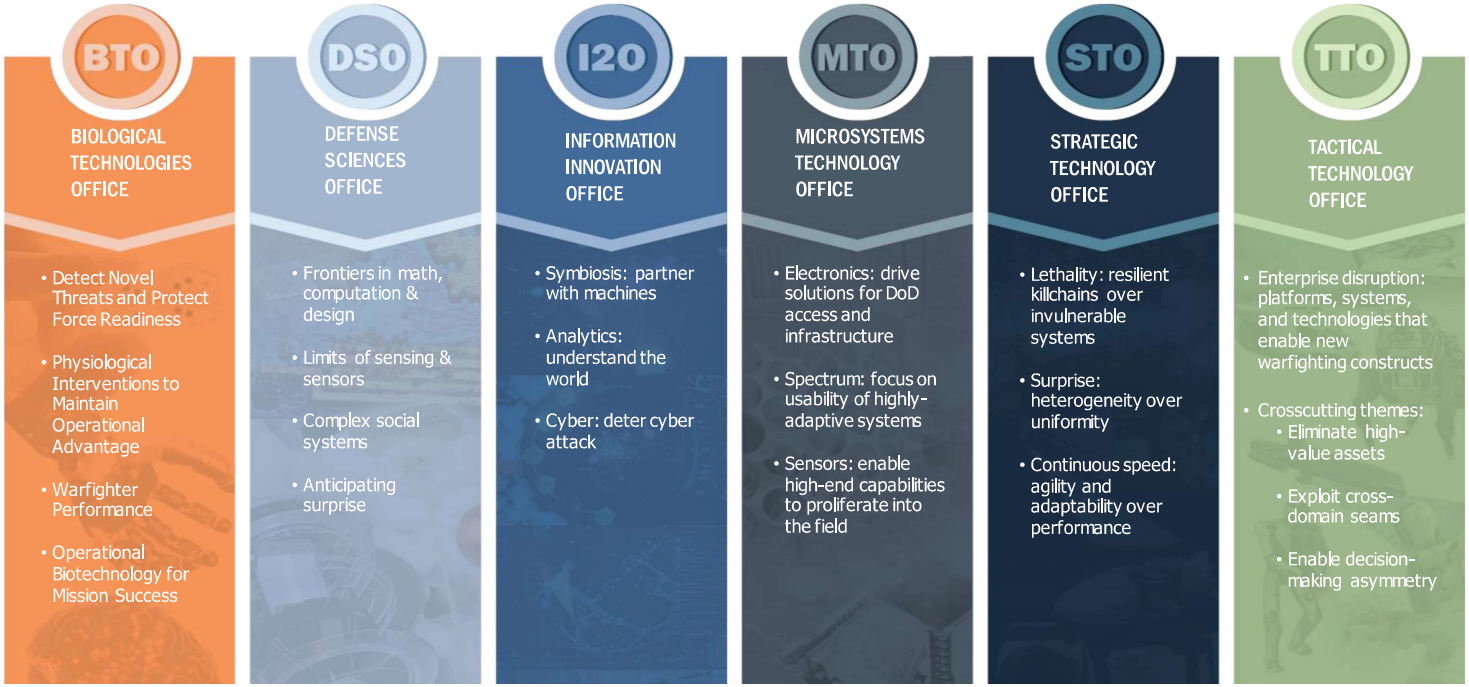
1984: X-29 Aircraft

2013: Blast Gauge

1960s | **1970s** | **1980s** | **1990s** | **2000s** | **2010s** | **2020s**



DARPA Technical Offices



BTO Thrust Areas: Pushing Biological Boundaries

The Heilmeier Catechism

DARPA operates on the principle that generating big rewards requires taking big risks. But how does the Agency determine what risks are worth taking?

George H. Heilmeier, a former DARPA director (1975-1977), crafted a set of questions known as the "Heilmeier Catechism" to help Agency officials think through and evaluate proposed research programs.

1. What are you trying to do?
2. How is it done today, and what are the limits of current practice?
3. What is new in your approach and why do you think it will be successful?
4. Who cares? If you are successful, what difference will it make?
5. What are the risks?
6. How much will it cost?
7. How long will it take?
8. What are the mid-term and final "exams" to check for success?

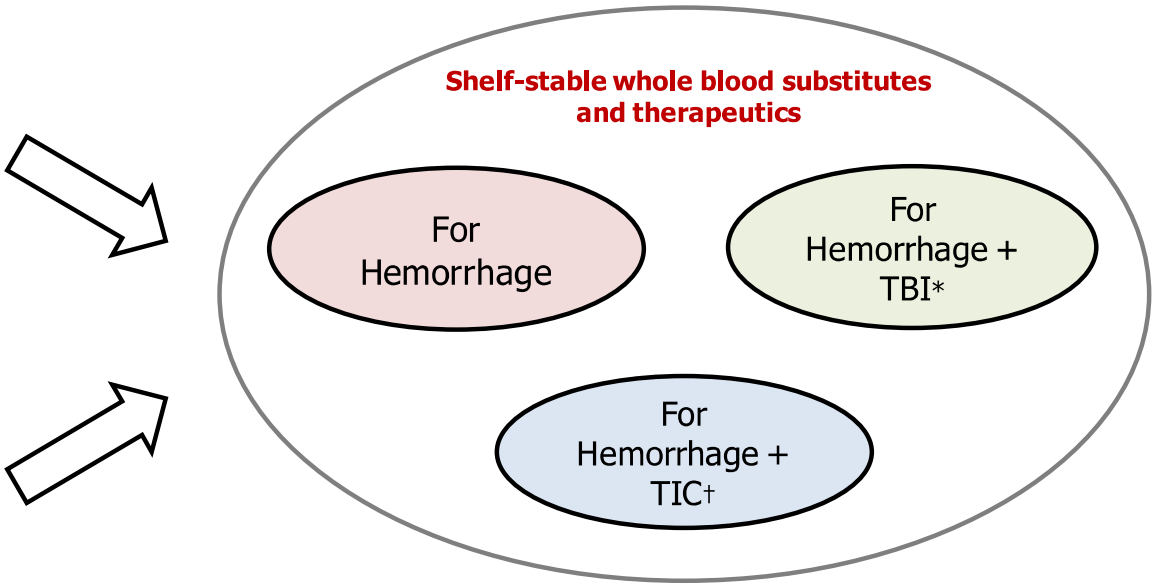
Fieldable Solutions for Hemorrhage with bio-Artificial Resuscitation Products (FSHARP)

FSHARP

DoD Problem: The DoD faces challenges in replacing lost blood in forward settings, which could become even more significant in prolonged field care and mass casualty scenarios.

Trauma and hemorrhage in austere environments without immediate MEDEVAC

Military medical support for civil mass casualty response



BTO Vision: A field-deployable, shelf-stable whole blood substitute as a hemorrhage countermeasure to sustain warfighters and civilian casualties in austere, pre-hospital settings.

*TBI – Traumatic Brain Injury
†TIC – Trauma-Induced Coagulopathy

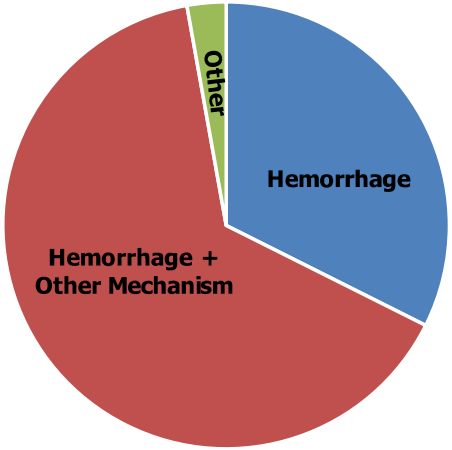
DoD relevance

Enhancing pre-hospital field care in combat, expeditionary, and civil support missions

FSHARP

Combat casualty care

USSOCOM potentially survivable deaths, 2001-2018

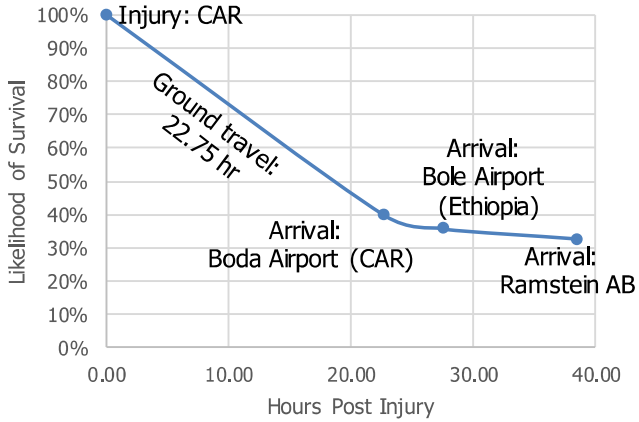


Adapted from: Mazuchowski et al., J Trauma Acute Care Surg 2020.

Most potentially survivable fatalities include a hemorrhage mechanism of death.

Ratios of medics or doctors:warfighters can range from 1:20 to 1:~1000

Notional MEDEVAC From Central African Republic to Landstuhl Regional Medical Center (Germany) for definitive care



Adapted from: Mouton et al., 2019.

- Closest Role 2 and higher facilities may be more than a day away.
- Immediate MEDEVAC may be impossible in peer and near peer conflicts.
- Likelihood of death increases with delayed and/or prolonged MEDEVAC.

Civil support missions

Civilian medical resources may be overwhelmed in natural disasters, accidents, attacks.

USAF photo by Staff Sgt. Quinton Russ
https://archive.defense.gov/home/features/2006/2005yearinreview/article4.html

2005 Pakistan earthquake: "Only three blood banks had refrigerators, but with limited storage capacities. A complete breakdown of infrastructure coupled with frequent power failures posed a serious threat to safety of the blood. . . Requirement of blood was high, but availability was limited." Mujeeb et al., Emerg Med J 2007.

Approach

FSHARP

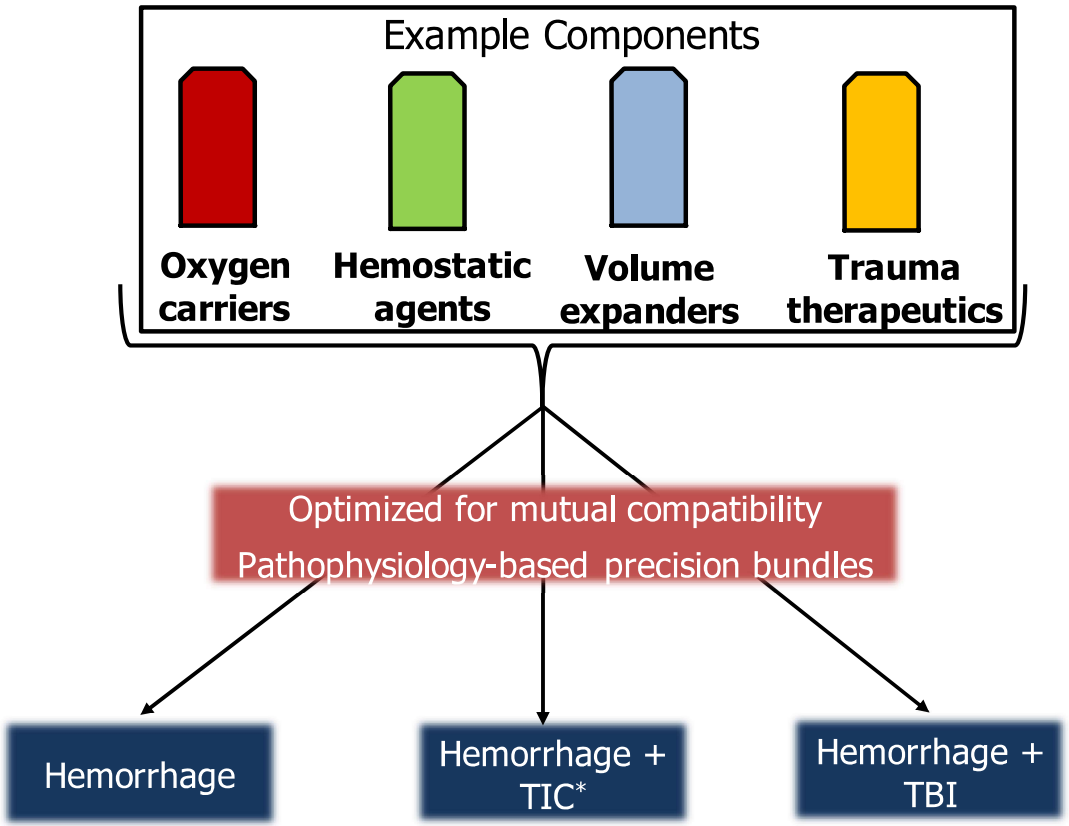
Trauma resuscitation products for settings where whole blood is unavailable

- Provide key functionalities of whole blood in trauma resuscitation.
- No cold requirement.
- Shelf-stable for months.
- Compact, lightweight.
- Rapidly reconstituted when needed.

DoD Benefit

- ❑ Life-saving resuscitation where blood supply is inadequate: far forward, delayed MEDEVAC, mass casualty.
- ❑ Stockpiled product to mitigate risk from donation reductions (e.g., pandemic).
- ❑ Modular approach enables precision treatment for trauma physiologies.

Modular components with adaptable synthetic/semi-synthetic design



*TIC, Trauma-induced coagulopathy.

Program Metrics

	Phase I: Development and Initial Demonstration		Phase II: Optimization and Complex Trauma Applications	
	Year 1	**Year 2**	**Year 3**	**Year 4**
Demos	Mid-Phase Demo: Month 12	End of Phase Demo: Month 20	Mid-Phase Demo: Month 36	End of Phase Demo: Month 45
Models	*In vitro/ex vivo* models (e.g., organs on chip)	Small/Large animal models of hemorrhage	Large animal models of hemorrhage + TBI or hemorrhage +TIC	Large animal models of hemorrhage + TBI and hemorrhage +TIC
TA 1	• Physical* parameters for each component in the combination within 10% of pre-combined component • Functional† measures within 40% of whole blood • Safety‡ measures within 10% of whole blood	• Functional measures within 30% of whole blood • No safety anomalies	• Demo in 2 trauma models (H, H+TBI, or H+TIC) • Functional measures within 20% of whole blood • No safety anomalies	• Demo in 3 trauma models (H, H+TBI, and H+TIC) • Functional measures within 10% of whole blood • No safety anomalies
TA 2	• 10 units in ≤4 weeks • Storage for 1 month at 4 and 25 °C: functional measures ≤ 30% ↓	• 50 units in ≤4 weeks • Storage for 1 month at 4, 25, and 40 °C: functional measures ≤ 20% ↓	• 50 units in ≤2 weeks • Storage for 3 months at 4, 25, and 40 °C: functional measures ≤ 20% ↓ • Cost ≤ 2x whole blood	• 50 units in ≤1 week • Storage for 6 months at 4, 25, and 40 °C: functional measures ≤ 10% ↓ • Reconstitution w/o mechanical agitation • Cost ≤ 1x whole blood • Weight w/reconstitution fluid ≤ whole blood

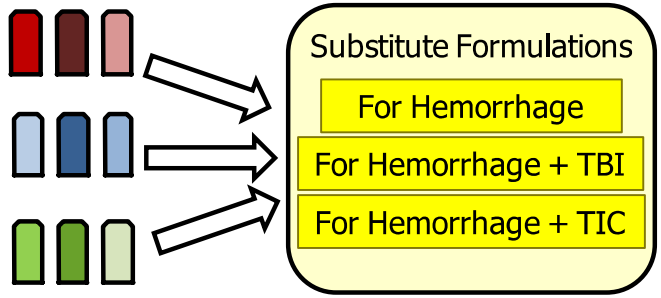
*Physical: E.g., size, shape, surface.
†Functional: E.g., hemodynamics, oxygenation, hemostasis.
‡Safety: E.g., Immune activation, off-target clotting, NO inhibition.

www.darpa.mil

Technical areas

FSHARP

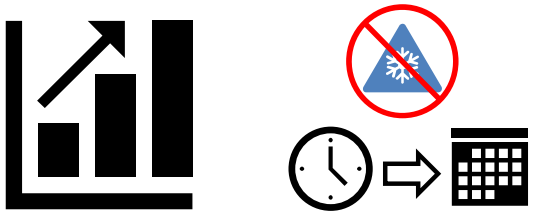
TA1
Blood Substitute Development



- Synthetic/semi-synthetic components that perform the critical functions of blood in trauma resuscitation.
- Bundles of co-administered components for specific clinical trauma pathophysiologies.

TA1 Components

TA2
Methods for Manufacturing and Stabilization



- Formulations and methods compatible with scale-up to meet DoD needs.
- Rapidly re-constituted and administered.
- Shelf-stable without cold requirement.

Deliverable: Bio-artificial blood product substitutes that are safe and achieve near parity to natural whole blood functionality.

Deliverable: Processes, preservatives, and apparatuses capable of consistent, timely production of shelf-stable TA1 products.

FSHARP Milestone Testing and Independent Validation & Verification (IV&V)

	Phase I: Development and Initial Demonstration		Phase II: Optimization and Complex Trauma Applications		Phase III: IND* Submission
	Year 1	Year 2	Year 3	Year 4	Year 5
Trauma Presentation	Hemorrhage	Hemorrhage	Hemorrhage+TBI or Hemorrhage+TIC	Hemorrhage+TBI and Hemorrhage+TIC	Hemorrhage, Hemorrhage+TBI, and Hemorrhage+TIC
Performer Model	In vitro/ex vivo models (e.g., organ-on-chip)	Small or Large Animal Model	Large Animal Model	Large Animal Model	Large Animal Model
IV&V Model	In vitro/ex vivo model	Small or Large Animal Model	Large Animal Model	Large Animal Model	N/A

NOTE: Phase III contingent on Phase II progress and resource availability.

*IND- Investigational New Drug

Program Schedule Overview

FSHARP

	Phase I: Development and Initial Demonstration		Phase II: Optimization and Complex Trauma Applications	
	Year 1	**Year 2**	**Year 3**	**Year 4**
TA1: Blood Substitute Development	Blood substitute development		Demo efficacy against hemorrhage + additional injuries	
TA2: Manufacturing and Stabilization	Manufacturing process development		Optimization for scale-up	
	Stabilization method development		Optimization for long-term stability	
Demonstration Models	*In vitro/ex vivo* models	Small/large animal models	Large animal models	Large animal models
Milestones		**Milestone Demo 1**; **Milestone Demo 2**	**Phase II go/no-go decision**; **Milestone Demo 3**	**Milestone Demo 4**
Regulatory Engagement	FDA Informational Meetings		FDA IND Pre-Submission	

Program Schedule Overview

FSHARP

Phase III: IND Submission

	Year 5
TA1: Blood Substitute Development	*In vivo* demo of no adverse effects Additional IND-enabling studies
TA2: Manufacturing and Stabilization	Demo of GMP manufacturing and scale-up suitable for clinical studies
Demonstration Models	Large animal models
Milestones	**Milestone Demo 5**
Regulatory Engagement	FDA IND Pre-Submission → **IND Submission**

Program Metrics

	Phase III: IND Submission
	Year 5
Demos	End of Phase Demo: Month 59
Models	Large animal models of hemorrhage, hemorrhage + TBI, and hemorrhage + TIC
TA 1	• *In vivo* demonstration of no adverse effects • Additional IND-enabling studies as required
TA 2	• Demonstration of GMP manufacturing and scale suitable for clinical studies