RBC-Factory

Christopher J. Bettinger, PhD



Proposer's Day

January 7, 2025



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DoD Problem: Dangerous environments degrade performance and endanger warfighter health



Rationale: Red blood cells (RBCs) are ideal carriers of countermeasures **Concept: Modify Host RBC RBC are <u>abundant</u> & <u>persistent</u>** Pre-RBC (vulnerable) Isolate host red Natural host blood RBC RBC Modified RBC (w/ Return new component) modified **Modified RBC** RBC Post-RBC (protected) 8 um <u>Device-based approaches</u> to introduce components The blood has ~1.5L of RBC & RBC circulate into mature RBC from host for ~ 120 days

Vision: Establish the physical and biochemical limits of cargos which can be inserted into RBC via nongenetic means





SoA: Pharmaceutical interventions (Rx) or donning personal protective equipment (PPE) **Personal Protective Equipment (PPE) Prophylaxes or Treatments (Rx) Mosquitos** Hypoxia Arctic Malaria **Extreme Cold** Hypoxia Malarone **Off Label Rx** Diamox O₂ masks **CTAPS** DEET Changes tissue Anti-malaria med. Experimental only Delivers 100% O₂ Mosquito spray Cold operations pH • Only reduces • Side effects^a: • N/A • Consumable Transient • Bulky & heavy dizziness & Cumbersome • Partially effective Reduces operator symptoms • Adherence? depression Logistical burden • Potentially toxic performance

Problem: These methods have poor efficacy and burden the warfighter (physical & cognitive)

SoA – State of the Art; PPE – Personal protective equipment; **Rx** – *Therapeutic;* **DEET –** *N,N-diethyl-meta-toluamide;* **CTAPS -** *Cold temperature and artic protection systems*

a – 10% of the population exhibits significant side effects





BLUF: Proteins can be attached to RBC surfaces...but they reduce circulation time & can detach

Surface modification of RBC^a

Cell "Backpacks"

Can stably attach colloids at scaleFlexible material compositions

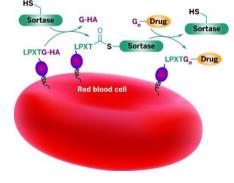
J. S. Brenner, et al. Annu Rev Biomed Eng 2021

Enzymatic conjugation

 Uses enzymes to conjugate proteins & peptides on cells using chemistry

J. Shi, et al. Proc Nat Acad Sci USA 2014

5 um



Key Limitations with SoA

- **1. Circulation time is reduced** by >80% (~1-2 weeks)
- 2. Component can detach from the surface (shear forces or enzymes)
- **3. Limited amounts** of new component can be attached
- 4. Processes are not scalable in a compelling or economically viable manner

a – Innovations attributed to Blood Pharming DARPA program

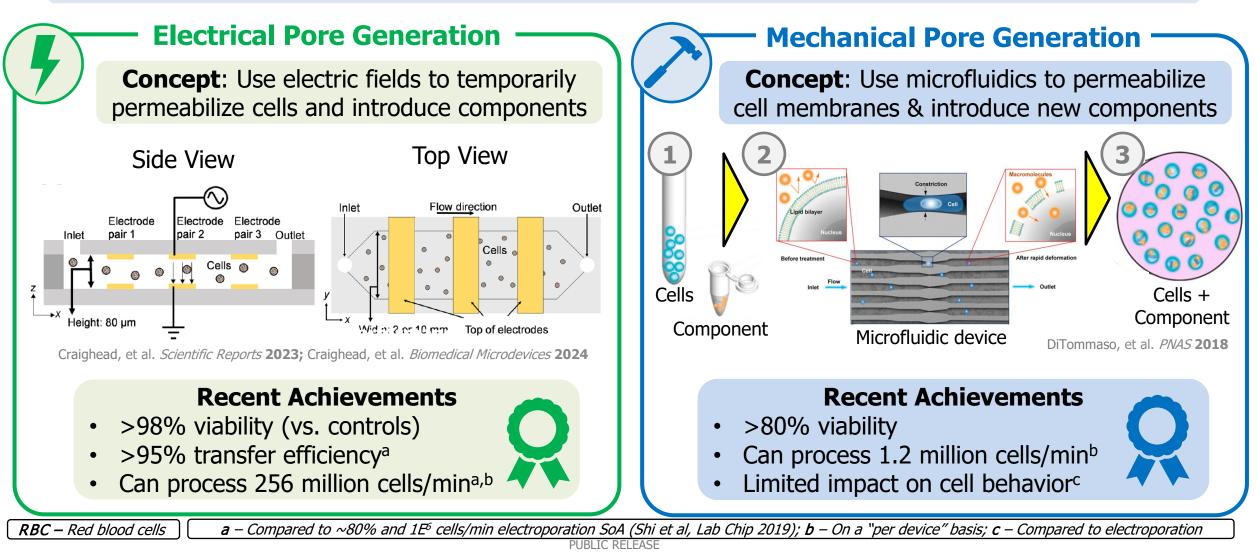
RBC – Red blood cells; SoA – State of the Art

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BLUF: Proteins and other biologically active components can be integrated with RBC



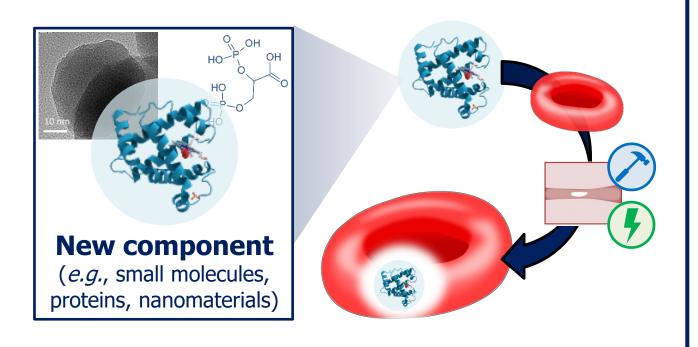




Open Scientific Questions & Key Technical Challenges

- **1. How much** of the new component can we integrate into an RBC?
- 2. What types of new components can we integrate?
- **3.** How fast can we integrate new components into RBC?
- 4. What effect does component integration have on <u>RBC properties & physiology</u>?

Performer Problem Set & Design Space -



- Stably integrate any protein, peptide, material into RBC
- Integrate enough component and process at scale
- Minimize impact on RBC structure & function





BLUF: The following parameters (and ranges) comprehensively describe the physical & chemical characteristics of molecules and materials to be inserted into RBC

	Parameter (factor)	Symbol	Range	Units	# logs
Molecules (compounds, proteins, & polymers)	Hydrodynamic radius	rH	[0.1, 100]	nanometers	3
	Mass-to-charge ratio	m/z	$\pm [10^2, 10^4]$	kg/Coulomb	2
	Molecular weight	Mw	$[10^2, 10^6]$	grams/mole	4
	Hydrophobicity	In[P] _{ow}	[-1, 5]	{ }	6
	Parameter (factor)	Symbol	Range	Units	# logs
Materials	Parameter (factor)Hydrodynamic radius	Symbol rH	Range [0.1, 100]	Units nanometers	# logs 3
(particles,		_			
	Hydrodynamic radius	rH	[0.1, 100]	nanometers	

RBC – Red blood cell; **In[P]ow** – Log of the partition coefficient between 1-octanol and water; **kg** – kilograms; **mJ** – milli-Joules

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BLUF: Fractional factorization will analyze all component properties in <u>18 experiments*</u>

* Taguchi L9 array can survey 4 factors across 3 levels each (low/hi end of range + 1 intermediate value) in 9 experiments

- This exercise will be repeated across (a) molecules and (b) materials (18 experiments total)
- This experimental burden is reasonable given the scope/scale of the RBC Factory timeline

			9		
Experiment Number	1	Colu 2	mn 3	4	
1	1	1	1	1	
2	1	2	2	2	
3	1	3	3	3	Wet la
4	2	1	2	3	experi
5	2	2	3	1	
6	2	3	1	2	
7	3	1	3	2	
8	3	2	1	3	
9	3	3	2	1	

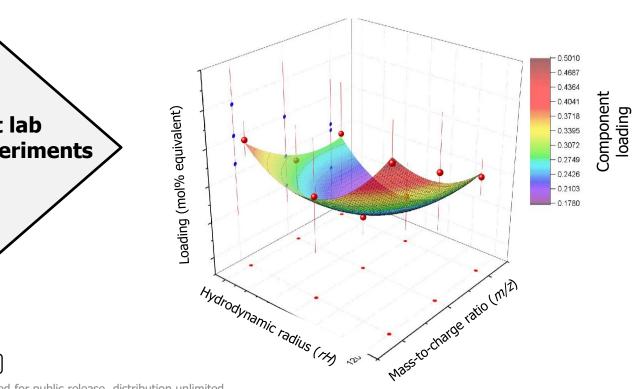
DOE Input – Taguchi L9 array

• Columns denote different factors (e.g., *Mw*, *rH*)

• Three levels are represented as "1, 2, or 3"

DOE – Design of experiments; Mw – Molecular weight; rH – Hydrodynamic radius









Key scientific questions that inform metrics	 How much of the new component can we integrate into RBC? What are the limitations on physical properties^a of components? Can modified RBC be produced at scale? Can modified RBC be biologically equivalent to host RBC?

	Category	Metric	Rationale	
Platform Metrics	Component Integration	 8 picograms of novel component per cell^b >95% of the component after 40 days <i>in vitro</i> 	 Introduce novel components into RBC at suitable concentrations Show [RBC+component] is stable 	
	Cell Fitness & Safety	• Circulation time: $\pm 10\%^d$ • Inflammation & immunity biomarkersc : $\pm 10\%^d$ • Clotting time & hemostasis: $\pm 10\%^d$ • Equivalent -omic profile to host RBC($\alpha = 0.05$)	 Show modified RBC are equivalent to host RBC 	
	Scalable Processing	• Modify >1x10 ⁹ cells per minute per device ^e	 Push the limits of throughput to modify RBC at scale^a 	
RBC - Red L	BC – Red blood cell; Hb – Hemoglobin BC – Red blood cell; Hb – Hemoglobin Compared to natural host RBC; e – Cell modification module <10 cm x 10 cm x 10 cm;			





Assessing acceptance, adherence and equity impacts

Expert Analysis and Perspectives



Responsible Communications

Active anticipation of perception issues

Platform Impact Assessment



Historical impact assessment



Criteria development



Stakeholder engagement

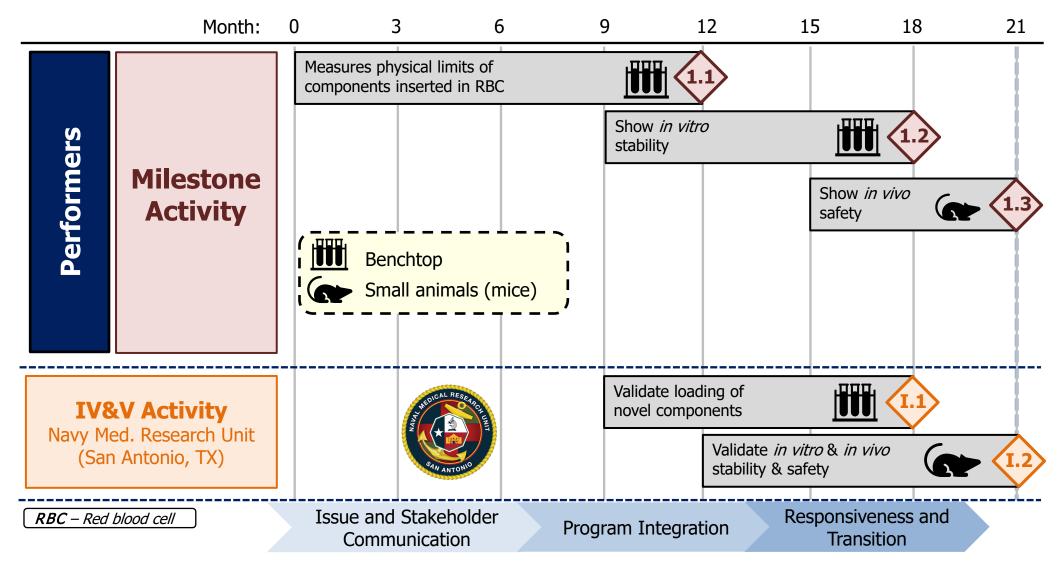


Impact assessment design



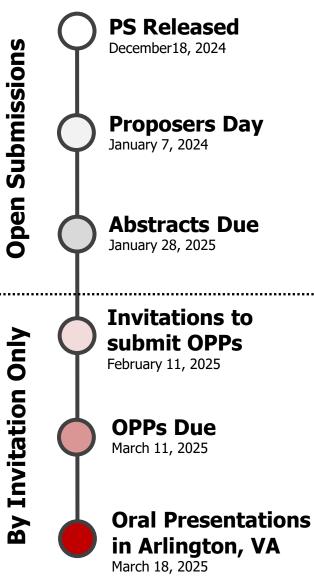
Program schedule & milestones











Critical Considerations

- The award vehicle will be an Other Transaction for Prototype (OT) with Milestone Payments
- The Oral Presentation Package (OPP) phase is by DARPA's Invitation ONLY

Tips for Successful Submission

- <u>Read the Program Solicitation (PS) carefully</u>
- Email questions to RBC-Factory@darpa.mil before January 26, 2025
- Form complete teams with comprehensive expertise & capabilities
 - Teaming is strongly encouraged
 - Industry expertise desirable
 - Teams are encouraged to have a program coordinator/project manager
 - There is no bias for teams internal to one institution or across multiple institutions, but effective communication and collaboration between teams is key



Proposal Evaluation Criteria All Criteria Must Be Addressed





Overall Scientific and Technical Merit

Technical approach is **innovative**, **feasible**, **achievable**, **complete and supported by a proposed technical team** that has the expertise and experience to accomplish the proposed tasks



Potential Contribution and Relevance to the DARPA Mission

DARPA's mission is to make pivotal early technology investments that create or prevent strategic surprise for U.S. National Security

T

Cost Realism

Costs are realistic for the technical and management approach and **accurately reflect the technical goals and objectives** of the solicitation.



Schedule Realism

The proposed schedule aggressively pursues performance metrics in the **shortest timeframe and accurately accounts** for that timeframe. The proposed schedule **identifies and mitigates** any potential schedule risk.





Data sharing

Proposers must include the description of a plan to share information with DARPA, RBC Factory IV&V teams and U.S. Government stakeholders

Animal Care and Use Review Office (ACURO)

All United States Department of Defense (DoD) funded research involving laboratory animals **must be reviewed for compliance with Federal and Department of Defense (DoD) Animal Care and Use Review Office (ACURO)** and approved by the Office of Research Protections (ORP).

You will not be allowed to initiate animal work until you receive approval from the Animal Care and Use Review Office (ACURO).

Ethical, Legal, and Societal Implications (ELSI)

Proposers should address potential ethical, legal, and societal implications of the proposed technologies. Program developments will be discussed with a **panel of expert external advisors** with expertise in bioethical issues, including human gene modulation.



Contracting (CMO) and Program Solicitation (PS)

Doing Business with DARPA

RBC-Factory Doing Business with DARPA

Lydia Richards Contracting / Grants / Agreements Officer DARPA Contracts Management Office

January 27, 2025





- Program Solicitation (PS) is posted at SAM.gov
- Pay attention to due dates (first page) and special instructions (Section 4)
- Award Instrument Type Other Transaction (OT) for Prototype Agreement
- <u>Important Dates</u>:
 - Posting Date: December 18, 2024
 - Proposers Day: January 7, 2025
 - Questions Due Date: January 10, 2025, 11:59 PM Eastern Time
 - Abstracts Due Date and Time: January 28, 2025, 12:00 PM Eastern Time
 - Oral Proposal Package (OPP) Due Date and Time: March 11, 2025, 12:00 PM Eastern Time
 - Oral Proposal presentations: March 18, 2025



- The Government reserves the right to award an OT for Prototypes under 10 U.S.C. § 4022, or make no award at all.
- Not a Request for Proposal (RFP)- FAR Part 15 does not apply
- Not a Broad Agency Announcement (BAA)- FAR Part 35 does not apply.
- OT Authorities were created to give DOD the flexibility necessary to adopt and incorporate business practices that reflect commercial industry standards and best practices.
- OTs can help encourage streamlined and cost effective project design and execution.
- OTs foster building of new relationships and collaboration in innovative arrangements.
- DARPA's use of an OT is to attract companies, traditional and non-traditional, to effectively negotiate business terms outside the FAR/DFARS based government acquisition process.



Use of OTs for Prototype

- 10 U.S.C 4022 (d) (1) permits DARPA's OT authority to be used only when one of the following conditions are met:
 - (A) There is at least one nontraditional defense contractor or nonprofit research institution participating to a significant extent in the prototype project;
 - (B) All significant participants in the transaction other than the Federal Government are small businesses (15 U.S.C. 638)) or nontraditional defense contractors;
 - (C) At least one third of the total cost of the prototype project is to be paid out of funds provided by sources other than the Federal Government; or
 - (D) The senior procurement executive for the agency determines in writing that exceptional circumstances justify the use of a transaction that provides for innovative business arrangements or structures that would not be feasible or appropriate under a contract, or would provide an opportunity to expand the defense supply base in a manner that would not be practical or feasible under a contract.



10 U.S.C 3014 Non-Traditional Definition:

- nontraditional defense contractor, with respect to a procurement or with respect to a transaction authorized under section 4022 of this title, means an entity that is not currently performing and has not performed, for at least the one-year period preceding the solicitation of sources by the Department of Defense for the procurement or transaction, any contract or subcontract for the Department of Defense that is **subject to full coverage under the cost accounting standards** prescribed pursuant to section 1502 of title 41 and the regulations implementing such section. To be considered as participating to a significant extent, the proposal should substantiate that the effort being performed by the nontraditional defense contractor is critical to the technical success of the project
- Participating to a significant extent or Significant Contribution means The contribution causes a material reduction in the cost or schedule or increase the performance of the prototype. The nontraditional performer is responsible for a key component, technology or process without which the prototype cannot be successfully developed (ie, on the critical path).



- RBC-Factory is using a modified acquisition approach to lower the administrative burden of entry, reduce program risk, foster competition, and have performing teams get to work quickly.
- Will be soliciting independent abstract submissions for RBC-Factory (21 months).
- A subset of submitted abstracts will be invited to submit Oral Proposal Packages and give oral presentations of their proposals. Selected proposers may be awarded an Other Transaction (OT) for Prototype Agreement. DARPA has approximately \$18.1M total for performer awards and anticipates making multiple awards.



- Abstracts are <u>REQUIRED</u>. Proposers must submit an abstract in response to this solicitation to be eligible to participate in the next acquisition step.
- The Government Evaluation Team will review submitted abstracts and invite selected performers to submit an Oral Proposal Package and give an Oral Presentation. Oral Proposal Packages <u>MAY</u> <u>NOT</u> be submitted without an invitation from DARPA.
- **Carefully review:** Goals/ metrics, Schedule of Milestones and Payments, required abstract content, evaluation criteria, and templates.
- Monitor SAM.gov for potential PS amendments and Frequently Asked Questions.



- Oral Proposal Packages **MAY NOT** be submitted without an invitation from DARPA.
- To expedite the award process, pay additional attention to the Cost Spreadsheet (Attachment D) and following Model OT for Prototype Agreement attachments:
 - Attachment 1: Task Description Document (Statement of Work for OTs), Describe the work that is being done; can use the Schedule of Milestones as a guide.
 - Attachment 3: Schedule of Milestones and Payments complete PS Attachment E
 - Attachment 5: Equipment
- Oral Presentations (40 min, 20 min Q&A) are planned to take place in the Washington, DC area. Virtual presentations are possible.
- After the oral presentations, DARPA will make a determination as to which proposers may be asked to participate in the program.
- Carefully read the PS Proposer Submissions that fail to comply with all requirements of the PS and/or subsequent proposal instructions may be deemed non-conforming and may be removed from consideration.
- Monitor SAM.gov for the final PS posting and potential amendments prior to proposal submission.



- All responsible sources capable of satisfying the Government's needs may submit a proposal that shall be considered by DARPA.
- <u>Non-U.S. organizations and/or individuals</u> may participate to the extent that such participants comply with any necessary nondisclosure agreements, security regulations, export control laws, and other governing statutes applicable under the circumstances.
- <u>Government agencies/labs & FFRDCs</u> are highly discouraged from proposing against this solicitation as awards to UARCs or FFRDCs will only be made by exception. UARCs and FFRDCs interested in this solicitation, either as a prime or a subcontractor, should contact the Agency Point of Contact (POC) listed in the Overview section prior to the proposal (or abstract) due date to discuss potential participation as part of the government team or eligibility as a technical performer.
- Organizational Conflicts of Interest
 - DARPA policy: Without prior approval or a waiver from DARPA, a contractor cannot simultaneously provide scientific, engineering, technical assistance (SETA) or similar support (A&AS) and also be a technical performer.
 - Must address in your proposal if providing SETA or similar support to any DARPA technical office(s) through an active contract or subcontract.



- No common Statement of Work Abstracts and Oral Proposals are evaluated on individual merit and relevance as it relates to the stated research goals/objectives rather than against each other.
- Upon review of Abstracts, the Government may elect to invite all, some, or none of the proposers to submit Oral Proposal Packages.
- Oral Proposals will be evaluated for strengths and weaknesses relative to the criteria published in the PS.
- The final evaluation criteria and oral proposal instructions will be included with the invitation to present an oral proposal. Evaluation criteria in instructions may very slightly from what is published in the PS.
- Government anticipates making multiple awards.
- The DARPA contracting office will contact the selected performers and begin the negotiation process.



- DARPA policy is to treat all submissions as competition sensitive, and to disclose their contents only for the purpose of evaluation.
 - Restrictive notices notwithstanding, during the evaluation process, submissions may be handled by support contractors for administrative purposes and/or to assist with technical evaluation.
 - All DARPA support contractors performing this role are expressly prohibited from performing DARPA sponsored technical research and are bound by appropriate nondisclosure agreements.
 - Input on technical aspects of the proposals may be solicited by DARPA from non-Government consultants/experts who are strictly bound by the appropriate non-disclosure requirements.



- DARPA reserves the right(s) to:
 - Fund proposals in phases (aka options) for continued work at the end of one or more of the phases
 - Remove proposers from award consideration should the parties fail to reach agreement on award terms, conditions and cost/price
- The DOD can issue follow-on production efforts for projects directly relevant to the capability it wants to acquire or develop.
- The DARPA mission is to get capability into the hands of the warfighter, and we believe an OT is the best vehicle to deliver that mission.

RBC-Factory (RBC-F) Doing Business with DARPA

Program Solicitation (PS) Inbox and Submission

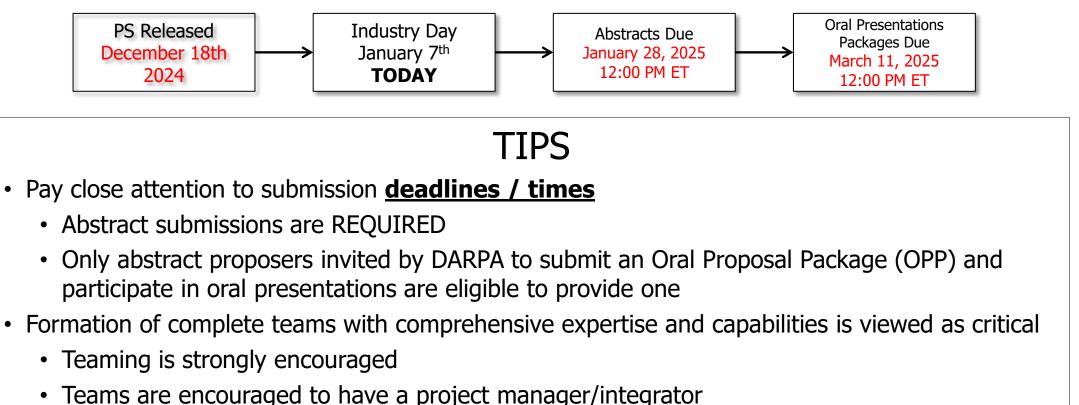
David Swan III PS Coordinator DARPA Biological Technologies Office

January 7, 2025





RBC-Factory Program Solicitation (PS) Timeline



Take advantage of today's opportunities to meet potential teammates



Direct ALL questions and communications to the PS Inbox: <u>RBC-Factory@darpa.mil</u>

Dr. Bettinger, any member of his team, or the PS Inbox cannot provide feedback or guidance on any aspect of your proposal; they can only clarify the content of the RBC-F PS

DARPA will update the RBC-F Q&A on a regular basis. The RBC-F Q&A can be found on the DARPA Opportunities web page

https://www.darpa.mil/research/programs/rbc-factory

All **questions must be submitted at least 3-5 days prior** to the abstract submission deadline in order to guarantee a response



Q: Do we have to submit a proposal abstract?

A: It is important to note that proposers must submit an Abstract in response to this PS to be considered for participation in the RBC-F program. Only abstract proposers invited by DARPA to participate in the oral presentations are eligible to provide one.

Q: Does DARPA anticipate awarding Cooperative Agreements or Procurement Contracts under?

A: No. The Government will review all oral presentations and selected proposers may be awarded an Other Transaction (OT) for Prototype agreement not to exceed \$8M.

Q: Our team intends to utilize an approach that modifies cell surfaces to achieve the RBC-F goals. Would this be of interest to DARPA?

A: No. See Section 1.2.4.B. of DARPA-PS-25-08 for a list including additional technologies that are not of interest and therefore considered out of scope for the RBC-F program.



Final bits of advice

Read the Program Solicitation (PS) over and over again, and follow all instructions carefully

A conforming proposal addresses **all aspects** of the PS

- Pay attention to "**must**", "**should**", "**shall**", and "**all**" in the PS
- Nonconforming abstracts may not be evaluated

DO NOT try to shoehorn ongoing, but not applicable, work into the PS

DO NOT submit a **rewritten USDA, NIH, or NSF abstract**

DO NOT propose to do anything that is **not directly relevant to the PS**

DO NOT submit **an irrelevant or incomplete abstract** in the hope we'll invite it anyway

A proposal abstract is **REQUIRED**



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Office-Wide BAAs

rogram-Specific BAA

Evaluation Process and

Resources for Responding to

Program-Specific BAAs

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Overview

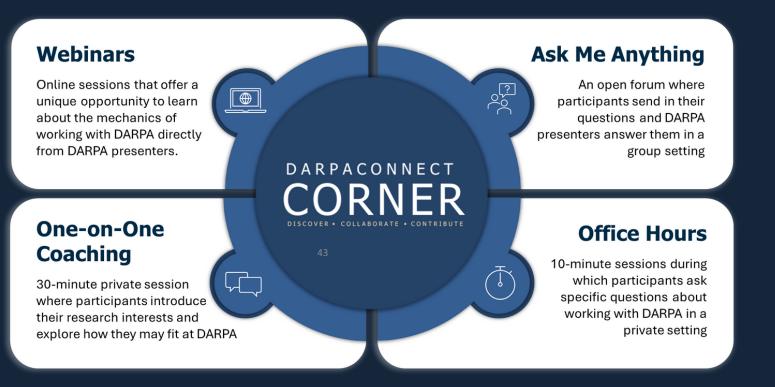
DARPA's Program-Specific BAAs are designed to solicit ideas that are tied to a specific area of interest. These solicitations are issued throughout the year as program managers develop new program ideas. This section will introduce you to the path through which a program is created, a sample program-specific BAA, and the average timeline to award.

The Path from Idea to Program

It is important to understand the DARPA path from an idea to a program. PMs welcome the opportunity during early ideation to learn from potential performers about problems and solutions of interest, as outlined in the interactive graphic below. In fact, many DARPA programs are initially sparked by conversations with potential performers.



Connect Corner





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Ethical, Legal, and Societal Implications



Intro to ELSI (Ethical, Legal, and Societal Implications)

Kerry Leehan, PhD Slides based on Dr. Rebecca Crootof's work as the DARPA 2024 Visiting ELSI Scholar

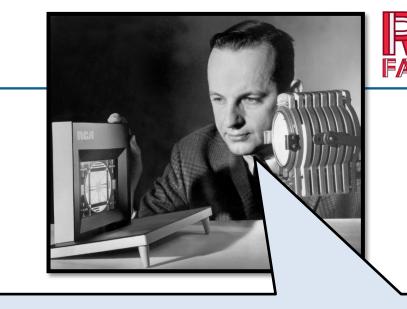
Briefing prepared for RBC-Factory Proposer's Day

January 7, 2025





- What is ELSI?
 - Improving research by identifying unknowns, anticipating consequences, and acting proactively to maximize benefits and minimize risks
- DARPA's "Year of ELSI" goals
 - Make explicit what is already happening implicitly
 - Expand the ways we think about programs and their impacts
 - Internalize the ELSI mindset



What are you trying to do?

How is it done today, and what are the [ethical/legal/social/technological] limits of current practice?

Who cares? If you are successful, what [ethical/legal/social/technological] difference will it make?

What are the risks?





Engagement to ensure safety and equity for military and civilian populations

Expert Analysis & Perspective

ELSI Performer Embeds

Proposers are encouraged to integrate their own experts into their proposed teams to collaborate with DARPA's ELSI experts, including dedicated resources for activities with the DARPA team.

Independent ELSI Group Members

ELSI Group members would not be eligible to propose as an interdisciplinary team member. Group will not be finalized until after teams have been selected for negotiation.





What are the benefits and opportunities?

- What does it facilitate or enable, alone or in combination with other technologies? In the near term? In the long term?
- Who enjoys the benefits?
- What technological/design choices promote the benefits?

What are the drawbacks and risks?

- What does it facilitate or enable, alone or in combination with other technologies? In the near term? In the long term?
- How might it be foreseeably misused?
- Who experiences the risks and harms?
- What technological/design choices minimize/eliminate the drawbacks?

What unknowns are anticipated?

 How can program structure and interdisciplinary teams mitigate the risks of unknowns?





- Be curious!
 - We're not answering questions today we're identifying them. And there are undoubtedly more that we didn't identify.
 - Goal is to promote an ELSI mindset for the duration of the program.
- Determine which (if any) opportunities you want to maximize or risks you want to alleviate via program design decisions.
- Determine which (if any) unknowns you want to evaluate during the program lifecycle and consider what data you could collect.
- Become more comfortable with stating, explaining, and documenting your design choices in light of ELSI considerations.

What are your takeaways?

Identify 1-3 takeaways from this discussion that will inform your program or design choices going forward.





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