DARPA-PS-26-02
Smart-Red Blood Cells (Smart-RBC)
Frequently Asked Questions (FAQs)

Last Updated: 11/07/2025
Updates are highlighted/underlined below

GENERAL INFORMATION

1. **My research is not geared specifically to meet the Smart-RBC program goals. Is there an alternate solicitation that I can respond to?**
   A: Yes. DARPA/BTO has an office-wide solicitation (HR001126S0003) for this purpose. Responses are being collected through September 30, 2026.

2. **How can I learn more about working with DARPA?**
   A: We recommend you take a look at DARPA Connect online at www.DARPAConnect.us and/or via email DARPAConnect@darpa.mil.

3. **Is Dr. Bettinger available for a call to discuss our proposed research?**
   A: Due to scheduling limitations, and in the interest of fairness to all proposers, Dr. Bettinger will not be taking program related calls and meetings. The best way to receive feedback on an approach is through the submission of a proposal abstract prior to the deadline specified in the Program Solicitation (PS). The PS describes the program, including metrics, in detail. Specific questions may be submitted by email to Smart-RBC@darpa.mil. Proposers should be aware that submitted questions and answers may be published on an FAQ page, with revisions to remove proprietary information.

4. **Will the Proposers Day slides be posted online?**
   A: Yes, information relayed during the Proposers Day will be made available on the BTO section of the DARPA Opportunities page: https://www.darpa.mil/research/programs/smart-rbc.

5. **Can foreign entities/organizations participate in the program?**
   A: Yes, non-U.S. organizations and/or individuals are eligible to submit an abstract/proposal to the Smart-RBC solicitation. Non-US individuals employed by US organizations and working in the US are allowed to participate on the Performer Team. Foreign National individuals that will be performing or attending meetings will be required to submit an eForm60.

6. **Can the executive summary in the abstract include a description of the proposed solution to clearly explain the goal and purpose of the Smart-RBC program?**
   A: Yes

7. **Attachment A template for this Smart-RBC effort requires that abstract submitters affirm "that the terms of the model OT agreement (Attachment B) are acceptable to the proposing organization without changes." Making this affirmation to accept terms and conditions at the *abstract phase* is unusual and removes the ability to further refine the Model OT, and tailor it to the relevant program. As a result, could we strike the Attachment A affirmation referenced above, and instead commit to negotiating terms and conditions in the event of award?**
   A: Proposers are permitted to remove the statement in Attachment A reading "[Prime Organization] affirms that the terms of the model OT agreement (Attachment B) are acceptable to the proposing organization without changes". Proposers will have the opportunity to propose

changes to the OT agreement at the OPP phase if they receive an invitation. Proposed changes may or may not be accepted by DARPA.

TEAMING

8. **Is teaming required? Is there a limit on team size? Is there a recommended team size? Can DARPA facilitate teaming if a proposer cannot address all aspects of the program on their own?**
   A: No to all four inquiries. Specific content, communications, networking, and team formation are the sole responsibility of the proposer team. Teaming profiles and lightning talks were distributed to Proposers Day registrants and are available upon request via email to Smart-RBC@darpa.mil. If you would like more information about working with DARPA, please go to the DARPA Connect webpage at www.DARPAConnect.us.

9. **Do all key personnel have to be identified prior to the submission of an abstract?**
   A: DARPA understands that final concepts and team make-up may change from abstract phase to oral presentation as the technical approach is solidified, however, please note that "Technical Ability" (as defined in Section 4.2 of the PS) is one of the evaluation criteria for proposal abstract submissions.

10. **Is an individual or organization able to submit more than one abstract in collaboration with different teams?**
    A: Yes. Teams can be primes or subcontractors on multiple proposals. If chosen for multiple awards, a clear path will need to be established to ensure no conflicts are present between the efforts. Proposers who are on multiple teams should be cognizant of the distribution of the level of effort across multiple awards and will be required to ensure that DARPA is only charged once for any potential duplicate efforts.

BUDGET/COST

11. **Is there any guidance you can provide on budget that's acceptable, and are costs like University overhead or general administrative costs like contribution towards technical support acceptable as a charge?**
    A: DARPA has approximately $35.1M in total for performer awards and anticipates making multiple awards. There are no predetermined or expected number of awards under Smart-RBC. Proposers should propose ambitious, yet achievable projects, and outline costs that are commensurate with what is required to achieve project goals and meet the program requirements.

12. **Would title to purchased equipment remain with the performer or the U.S. Government upon completion of the program? Furthermore, are replacements or upgrades of existing laboratory infrastructure/equipment considered allowable costs when required to meet program objectives? Is it acceptable to include budget for service charges for equipment maintenance?**
    A: If proposed equipment purchases are included in a negotiated award, those items would, subject to disposition procedures, remain with the performer. Please note that abstracts will be reviewed in accordance with the criteria listed in Section 4.2 of DARPA-PS-26-02, one of which is "Cost Rough Order of Magnitude (ROM)." The replacements/upgrades would need to therefore be "reasonable, realistic, and affordable for the technical approach and accurately reflects the technical goals and objectives of the Program Solicitation."

13. **How does DARPA intend to structure contracting and funding among performers, particularly for international teams? To be 100% sure: is there a preference or requirement for a U.S.-based**

lead organization, with non-U.S. partners participating as subawardees, or can non-U.S. entities serve as prime contractors in their own right?
A: DARPA has no preference (U.S.-based prime versus non-U.S. prime).

14. **Additionally, will DARPA execute a single prime award who manages all subcontracts, or does the agency plan to issue individual agreements directly to each performer for their portion of the program?**
A: Single award with each prime (Multiple awards are anticipated).

PROGRAM STRUCTURE

15. **How will the details of the computation and simulation resources, offered through the T&E partners, be organized?**
A: These computational and simulation resources will be offered to prospective performers after source selection. The specific assets made available will depend upon the capabilities and gaps of each performer. T&E resources are considered augmentative and a derisking asset. To that end, each team and their associated proposal should describe a comprehensive and standalone workflow that does not require specific capabilities from the T&E team.

16. **Does the Smart-RBC proposed solution align with RBC-Factory that require proteins to be transfected into the RBC; or is it preferred that it be separate? Would you prefer that we think through how the two programs would integrate, or would you prefer that we design the Smart-RBC to be independent?**
A: The Smart-RBC and RBC-Factory programs are separate and there should not be any overlap in proposed solution and no integration between the two. For more information about the differences between the two programs please see slide 15 of Dr. Bettinger's Smart-RBC Program & PS Overview found at https://www.darpa.mil/research/programs/smart-rbc.

17. **Does the Abstract/Proposal specifically need to address the Regulatory Engagements or Eligibility, Adoption, and Adherence Assessment sections of the program?**
A: Yes, proposers should indicate who on their team has the capability to respond to findings from DARPA-led Regulatory Engagements and EAA Assessments.

18. **Are there deadlines by which the safety metrics (Table 2) must be shown for Phase I/II?**
A: No, safety metrics must be completed by the end of each phase. Keep in mind that for risk mitigation, an early understanding of how RBCs may be affected is important.

19. **We appreciate from reading the proposal that specific circuits must be disclosed for evaluation; could DARPA confirm that flexibility exists for subsequent optimization or substitution within that design framework during Phase 1?**
A: On or before 15 months performers will submit a pull forward plan (PFP) due to DARPA to refine the biological circuit plan for Phase II. *Note: If a performer completes the milestones associated with Phase I prior to 15 months, they may be permitted to submit the pull forward plan (PFP) early and start Phase II before 18 months*.

20. **If our organization is awarded an OT for Prototype under the Smart-RBC program, will we be paid for each fixed milestone if we do not meet the program metrics?**
A: Payment will be received as long as the performer completes all the tasks in the task description document (TDD) corresponding to the milestone and have adequately reported the results. Milestones represent deliverables, not achievement of metrics.

TECHNICAL/METRICS

21. What are the requirements for the metric related to >10 proteins in Phase I?

A: The spirit of this metric is to explore what is possible with respect to engineered precursor cells that could differentiate into mature RBCs. To that end, prospective proposers can adopt a fairly liberal interpretation of this metric. We are primarily looking for >10 significant changes to the protein profile of natural RBCs. Examples include (but are not limited to): adding in new-to-RBC proteins, increasing the # of copies of proteins in mature RBC to non-natural levels; significantly reducing the # of copies of proteins in mature RBC to non-natural levels.

22. Do we need to use all >10 new proteins and/or modifications from Phase I in our biological circuit in Phase II?

A: Not necessarily. It may be possible to fulfill the metrics of the Sense, Decide, and Act without using all of the >10 new proteins and/or modifications from Phase I.

23. Are there requirements or preferences for what types of human cells can be used as starting material (including iPSCs)?

A: There are no restrictions or preferences on human cell types as long as there is a credible path to meeting the milestones and metrics outlined in the program.

24. Does the final engineered SRBC have to be fully mature?

A: We strongly prefer to have a fully differentiated and mature enucleated SRBC for both Phase I and Phase II. However, proposer's may describe approaches wherein enucleated reticulocytes can be delivered to a host. NOTE: The cells **must** be enucleated and have characteristics to minimize the risk of transferring genetic material to the host upon delivery.

25. What should be the capability of the final Smart-RBC circuit?

A: The final Smart-RBC circuit produced in Phase II and tested in the capability demo should address one of the two use-cases: Increased Exercise Tolerance OR Accelerated Hemostasis. Other use cases will **not** be considered for this program.

26. Are cell production and scaling in scope for the program?

A: Cell production and scaling are in scope to produce enough SRBCs for the capability demo. Large scale cell production beyond the needs of completing the CD are not essential to the program and thus considered out-of-scope.

27. Is gene editing required or are other solutions, such as transposases, acceptable?

A: Any manner of progenitor cell manipulation to develop SRBCs is acceptable.

28. Does each protein need to be introduced as its own edit, or is it acceptable to create multiple protein integrations so that fewer integrations are required?

A: No, each protein does not need to be its own edit.

29. Should final integration efficiency across all edits be 80% or should each individual edit be 80% efficient?

A: 80% for each individual edit. The goal of Phase I is to produce the maximal number of proteins (at least 10) with a yield compatible with future economic and production constraints.

30. Does the final Smart-RBC circuit in Phase II need to have both cytoplasmic and membrane proteins?

A: The final SRBC circuit in Phase II does not strictly need to contain both cytoplasmic and membrane proteins if an effective Sense, Decide, and Act circuit is generated.

31. Does the final Smart-RBC circuit need to have two "integrated" logic gates?

A: You must have at least two gates in the final Smart-RBC circuit in Phase II. The goal is to produce two logic gates that are new-to-RBCs. They must eventually work together within the decide and act layers of the circuit.

32. **Does the safety metric of +/-10% clotting time hold for circuits seeking to accelerate clotting in response to traumatic injury?**
A: If the goal is to improve clotting time (under the accelerate hemostasis goal), then the clotting time safety metric will no longer apply.

33. **Can the proposal use mouse RBCs or only human?**
A: The requirement is for human cells and test beds that are compatible with human cells.

34. **Do all safety metrics listed in Table 2 need to be completed in the program?**
A: No, Table 2 shows notional metrics and methodology to ensure SRBC safety and equivalency to natural RBCs. These metrics will be refined during source selection including decisions on exact tests to be completed, test markers, test beds, etc. Proposers should share which metrics (which can include additional metrics from those listed in Table 2) they are able to complete and how they would plan to do so.

35. **Can novel protein expression be constitutive?**
A: Yes.

36. **Do the two biomarkers in the Sense layer of the biological circuit need to be linked?**
A: No, it is not required for them to be linked. However, the idea is to provide redundancy in the circuit.

37. **What type of donor blood may be used?**
A: Proposals may use donor blood or blood products. Please review the chart in section 1.2.4 of the PS to ensure you understand the regulatory requirements for your proposal. Proposals must not contain clinical trials or direct human testing.

38. **For the Capability Demo (CD), is there a preference between in vivo or in vitro test beds?**
A: No preference is given to either in vivo or in vitro test beds for CDs so long as the approach is rigorous and properly justified. Test beds should be compatible with human cells.

39. **Can you explain your meaning behind a 1% Limit of Detection (LOD) for TC#1 (Table 1)?**
A: A 1% LOD means that the circuit can respond to a 1% biomarker concentration change relative to normal baseline physiology. For example, if baseline physiological concentrations are 100 nM, the sensor must be able to identify (at a minimum) an increase to 101 nM or a decrease to 99 nM.

40. **Following gene editing of human RBC progenitor cells, is it allowable to further modify the edited cells to produce mature RBCs?**
A: Yes.

41. **To minimize the risk of transferring modified genetic material to a prospective recipient, should strategies that use miRNAs or mRNA as the response elements be avoided?**
A: Any manner of progenitor cell manipulation is acceptable, including miRNAs or mRNAs. However, the final modified red blood cells must not contain modified genetic material or added machinery (including added miRNAs or mRNAs) which might pose significant risk to the host.

42. **With respect to the nature of the biological circuits regulating the sense-decide-act capabilities of the RBCs, is it important or required that the response be fully dynamic (e.g. OFF-ON-OFF) or can it be unidirectional (OFF-ON)?**
A: The SRBC sense-decide-act circuit can be unidirectional or fully dynamic.

43. **Could DARPA clarify whether the "Decide" element must represent an explicit logic or computational step, or whether direct *responsive circuits*—in which a sensed signal directly modulates an output without a separate decision module—would meet the program's intent? For example, would DARPA consider metabolite-responsive expression systems that directly trigger an adaptive protein or metabolic change to satisfy the "decide–act" criteria?**
A: No, there must be a decide element in the circuit. As seen in the metrics for TC#2 (Table 1), the circuit must contain a decide element with at least two logic gates and a switch ON-OFF ration of greater than 10x relative to normal baseline physiological values. Please also note there are also metrics listed in Table 1 for the sense and act portions of the circuit.

44. **Creating a SRBC may require aims such as developing universal donor blood or enhancing freeze–thaw recovery. Do these aspects need to be implemented via circuit-based approaches, or can alternative engineering strategies be responsive under the Smart RBC framework?**
A: The final SRBC only needs to contain 1 circuit which enables the final capability demo addressing one of the two use-cases: Increased Exercise Tolerance OR Accelerated Hemostasis. The final circuit must also meet the metrics outlined in Tables 1 and 2. Additional modifications can be proposed via any engineering strategy.