Request for Information:
DRIVe Anticoagulation in Extracorporeal Membrane Oxygenation Therapy

RFI-BARDA-21-0001

Division of Research, Innovation and Ventures
Biomedical Advanced Research and Development Authority
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Washington, DC 20201

www.DRIVe.hhs.gov

I. INTRODUCTION

The mission of The U.S. Department of Health and Human Services (HHS) Office of the Assistant Secretary for Preparedness and Response (ASPR) is to save lives and protect Americans from 21st Century health security threats. The Biomedical Advanced Research and Development Authority (BARDA) was established in 2006 to, through partnerships with industry, develop and procure medical countermeasures, vaccines, drugs, therapeutics, diagnostic tools, and non-pharmaceutical products, that address the public health and medical consequences of chemical, biological, radiological, and nuclear (CBRN) accidents, incidents, and attacks, pandemic influenza, and emerging infectious diseases. Specifically, BARDA supports the advanced development and procurement of drugs, vaccines, and other products that are considered priorities for responding to and recovering from threats to American national health security. The medical countermeasures and products in this diverse portfolio have received over 50 Food and Drug Administration (FDA) approvals, licensures, or clearances.

Preventing and protecting against new health security threats requires breakthrough solutions. To address these new threats, ASPR and BARDA launched The Division of Research, Innovation and Ventures (DRIVe). The mission of DRIVe is to accelerate innovations, and improve the availability of transformative technologies and countermeasures to protect Americans from natural and intentional health security threats. To that effect, DRIVe is building an ecosystem of restless innovators that includes investors, companies, and research teams offering solutions to a broad range of national health security threats and health challenges.

Additional information about DRIVe can be found at www.drive.hhs.gov

II. PURPOSE

DRIVe is seeking information on developments in anticoagulation drugs, assays, and management in the specific context of extracorporeal membrane oxygenation (ECMO) therapy. The intent is to identify areas of innovation that can solve the challenges posed by anticoagulation in ECMO or improve on the ways this issue is currently being addressed. BARDA will not execute any awards based on this notice. This RFI solely aims to gather knowledge on present and future capabilities and other pertinent marketplace data to strengthen BARDA's understanding of the current developmental landscape of this field. This does not constitute a Request for Proposal (RFP).

DRIVe has not committed to investing in technological advances in ECMO. However, pandemics and other public health emergencies may lead to increased hospitalizations and emergency response, and technological interventions such as ECMO could aid in critical care and clinical management of patients. BARDA is performing market research to better understand opportunities for investment within the landscape of anticoagulation in ECMO. This may enable the implementation of a strategic approach should BARDA decide to prioritize the development or acquisition of technology to advance

ECMO therapy.

III. BACKGROUND

Support for dysfunctional vital organs often relies on an extracorporeal vascular circuit. While experimentation with pumps and conduits began in the 19th century, two 20th century advances set the stage for support or replacement of organ function: the 1940s development of a semipermeable membrane suitable for the clinical exchange of water and small solutes and the refinement of membrane technology over the subsequent four decades to allow exchange of oxygen and carbon dioxide. These twin advances enabled complete (if temporary) substitution for renal, pulmonary, and cardiac function. They have also led to further innovation in clinical therapies, such as therapeutic apheresis and adsorption therapies. Extracorporeal circuits consist, at a minimum, of four elements: (1) vascular cannulae that partially dwell within the patient; (2) conduits that carry blood to and from site of extracorporeal handling; (3) the extracorporeal support that removes, exchanges, and/or returns a blood component; and (4) a pump that maintains flow.

All extracorporeal circuits challenge the delicate physiological balance that maintains blood as a fluid, e.g. exposure of whole blood to foreign surfaces activates several processes that culminate in clot formation. The usual approach to managing this balance requires anticoagulation, namely the use of chemical or biological agents that inhibit one or more aspects of coagulation. While anticoagulation is usually considered in the context of the patient (systemic anticoagulation), some implementations of renal dialysis focus on regional (circuit) anticoagulation, and a few strategies attempt to minimize conduit activation through chemical bondings and coatings.

None of these approaches to anticoagulation is entirely satisfactory. The normal balance between clotting and bleeding involves several interacting networks that act at the interface between blood and the tissue that contains it and also within the plasma. Anticoagulation requires perturbation of one or more aspects of these interacting networks. There are four general problems.

- First, the anticoagulation is insufficient to the need. Extracorporeal formation of clot interrupts flow and function, and reperfusion of even small clots often culminates in life threatening embolization.

- Second, anticoagulation can result in spontaneous hemorrhages, especially in the brain, and cause considerable morbidity and mortality.

- Third, anticoagulation is dynamic and must be frequently monitored and adjusted in order to minimize the risks of inappropriate clot formation and unwanted bleeding. Drugs that cause anticoagulation disrupt not only the coagulation network at their site of action, they also implicitly disrupt the various feedback loops that maintain normal balance.

- Fourth, the need for ECMO support is often accompanied by progressive dysfunction of other organ systems (for example, hepatic and renal). Since ECMO addresses only cardiac and pulmonary

dysfunction, managing anticoagulation can lead to unexpected adverse pharmacokinetics due to dependence on organ clearance and metabolism. This is further exacerbated by the fact that anticoagulation monitoring strategies are still largely episodic rather than continuous.

More generally, the management of anticoagulation during extracorporeal support is labor-intensive, imperfect, and prone to complication. Currently, all extracorporeal therapies require near-continuous supervision by professionals trained in management of anticoagulation and its complications.
That intense human oversight would be supported, improved, and possibly simplified not only by improved anticoagulation drugs, not only by mechanism-specific rapid anticoagulation assay, and not only by novel surface technologies, but also by use of closed loop titration of drugs enabled by artificial intelligence. BARDA believes that simplifying the management of anticoagulation of extracorporeal circuits with such innovations would lessen the need for high-skilled clinical staff to administer and could enable broader usage of ECMO and other therapies limited by coagulation. BARDA envisions a future in which ECMO could be conducted in ward settings, in which kidney hemodialysis could be conducted routinely at home, and so on.

IV. PROJECT REQUIREMENTS & OBJECTIVES

In this request for information, the public is invited to respond to the following prompts that are divided into new therapies and assays, management and automation, and material and design, as well as to share ideas that do not fit one of these prompts.

1.0 New therapies/assays:

1.1 The normal balance between clotting and bleeding is maintained by a delicate network that collectively regulates the activity of dozens of components including flowing blood elements (e.g. cells, platelets), plasma, and endothelial surface molecules. Systemic anticoagulation currently relies largely upon heparins and direct thrombin inhibitors, two drug classes that disable major components of that network. Moreover the assays of their effect—assays of the extent to which that network is compromised -- are imprecise and inconvenient. As a consequence, clinically serious derangements of the network—insufficient or excess anticoagulation states-- are often unnoticed until there is bleeding or clotting event. What other chemical or biological agents are currently being developed or evaluated to complement or replace these traditional methods?

1.2 Regional anticoagulation (often a citrate/calcium titration) has proven effective where flow rates are comparatively low (example, continuous renal replacement therapies) but have not been employed where the extracorporeal circuit demands high flow owing to challenges in titration efficiency and volumes of reagents required. Are there alternative approaches to regional anticoagulation potentially involving rapidly exchangeable small molecules such as dissolved gasses?

1.3 How does management of complementary problems—for example the formation of biofilms at the surface of indwelling cannulae—alter the tendency of blood flowing through or around those

cannulae to coagulate? More generally, could management of such problems materially affect the challenge of anticoagulation management?

2.0 Management and automation:

2.1 Management of traditional methods of systemic anticoagulation usually involves testing of coagulation capacity by diverse methods including exposure to solid material (activated clotting time), conventional lab tests (prothrombin time, activated partial thromboplastin time), direct effect measurement (such as anti -Factor Xa or 'heparin' level), and physical clot analyses (thromboelastography and viscoelastic coagulation testing). What, if any, alternatives are being developed or evaluated that would streamline testing and/or make the evaluation of anticoagulation status safer or more reliable?

2.2 Pumps are typically of continuous roller (lower flow, typically RRT) or centrifugal (higher flow, typically ECLS) design. Are there better pump programming options or better design options that would have an aggregate less disruptive effect on circulation and hence on the need for anticoagulation? For example, are there innovations that could reduce friction and heat generation that favor coagulation? Would there be less thrombogenesis with semi-pulsatile flow?

2.3 Are there strategies to separately address the risks of spontaneous hemorrhage that are caused by the need for anticoagulation but occur distant from the cannulation sites? For example, would—and how would—more precisely titratable reversal agents and the fine tuning they would enable affect the frequency and severity of bleeding and thrombosis?

2.4 What opportunities exist to automate the management of anticoagulation so that the current need for near continuous supervision and management might be lessened?

3.0 Material and design:

3.1 What opportunities exist to make (indwelling) vascular cannulae less thrombogenic? What refinements in coating or in physical design are being developed or evaluated to reduce the risk of coagulation or activation of coagulation during the brief transit from the intravascular site to the conduits?

3.2 Conduits, (including tubing, housings, and connectors) tend to have relatively slower flow velocities and prolonged surface contact. While heparin-bonding is approved, it is not universally used. Moreover, they seem to offer only transient benefit as those conduits undergo functional endothelialization and allow thrombogenesis. What opportunities exist to bond longer lasting alternative agents, or even to place catalytic agents to generate antithrombogactivities on these non-permeable surfaces?

3.3 The extracorporeal support—often a semipermeable membrane—is arguably the most critical element of the circuit. It typically requires rapid expansion of surface area to facilitate

removal/exchange/replacement of blood-borne substances, an expansion that not only slows flow (to permit the exchange) but also sharply increases the opportunity to initiate thrombus formation on exposed surface. At the same time, the exchange process must be reliable and efficient, typically involving countercurrent flow of gas or liquid on the other side of the membrane. What advances in material, architecture, bonding and embedding are in development or testing that could substantially reduce the thrombogenicity—and thus the need for anticoagulation—at this critical point in the extracorporeal circuit? Can anticoagulants be generated or locally infused with reversal prior to reperfusion?

Beyond the prompts above, what novel opportunities and approaches exist to minimize or eliminate the need for anticoagulation and thus remove one of the major barriers to expansion to these lifesaving methods?

V. CAPABILITIES STATEMENT AND INFORMATION SOUGHT

Respondents must provide, as part of their responses, a capability statement that fully describes their currently available technology including the level of analytical verification and clinical validation attained to date. The description shall include the Technical Readiness Level (see: https://www.medicalcountermeasures.gov/trl/integrated-trls/).

VI. SUBMISSION INSTRUCTIONS

All capability statements must provide the following:

1. Company name and address
2. Point of contact, email and phone number
3. Website
4. Business size and status (please include NAICS Code and DUNS if you have one)
5. Capability information in response to the project requirements and qualifications identified in this notice
6. Regulatory strategy
7. Engagements with the FDA
8. Non-clinical studies
9. Clinical studies

Respondents must provide documents on 8.5" by 11" inch pages, typed in a 12-point Arial or Times New Roman font (except for images), and limited to no more than 8 pages in a format compatible with Microsoft Office ® or Adobe® Acrobat®.

Responses must be submitted via email to DRIVeContracting@hhs.gov **by 11:00AM ET on May 18th, 2021** with the **Subject Line: "[Company Name] DRIVe Anticoagulation in ECMO Therapy Response to RFI"**. It is recommended that submissions are sent at least two hours in advance of the deadline to allow for any server delays.

VII. DISCLAIMER AND OTHER INFORMATION

BARDA encourages respondents to submit currently available information, to include links to online material, or to notify BARDA of the publicly available location. Respondents shall mark confidential, privileged, proprietary, trade-secret, copyrighted information, data, and materials with appropriate restrictive legends. BARDA will not publicly disclose proprietary information obtained as a result of this survey. Unless otherwise marked, the Government reserves the right to use information provided by respondents for any purpose deemed necessary and legally appropriate. BARDA will presume that any unmarked information, data, and materials were furnished with an "unlimited rights" license; assumes no liability for the disclosure, use, or reproduction of the information, data, and materials. By engaging in this process or submitting any information in relation to this RFI, interested parties acknowledge that federal and nonfederal U.S. Government personnel may participate in the process and provide input compliant with applicable law and regulation. All personnel are strictly bound by the appropriate non-disclosure requirements. Interested parties should not engage in any part of the announcement process if they do not consent to the participation of non-federal consultants as described in this subparagraph. Your response will become government property and the U.S. Government may publish some of its non-proprietary content.

Responses to this notice are not offers and cannot be accepted by the federal government to form a binding contract or issue a grant.

Respondents are advised that the Government is under no obligation to acknowledge receipt of the information received or provide feedback to respondents with respect to any information submitted.

VIII. INQUIRIES

All technical and administrative correspondence and questions regarding this announcement must be submitted via email to DRIVeContracting@hhs.gov **by 11:00AM ET on May 4th, 2021** with the **Subject Line: "[Company Name] DRIVe Anticoagulation in ECMO Therapy Questions to RFI".** Answers to relevant questions will be posted to the RFI on www.beta.sam.gov. Questions should not contain proprietary or classified information.

BARDA DRIVe cannot guarantee that questions received after 11:00AM ET on April 13th, 2021 will be answered.