Self-evolving and Adapting Therapeutics (ADAPT) RFI, DARPA-SN-15-54
**Responses due August 25, 2015 - 4:00 PM ET.**
POC: Jim Gimlett, DARPA/BTO; E-mail: DARPA-SN-15-54@darpa.mil
URL: http://www.darpa.mil/work-with-us/opportunities

**Background**

Over the past century, the industrialized and developing world has benefitted tremendously from therapeutic advances to treat a spectrum of diseases, from viruses, bacteria, and parasites, to malignant tumors. Most of these available therapies are chemical and biological compounds designed to treat the pathogen or disease in its state at the time of diagnosis. Even though many pathogens and diseases will undergo dynamic changes over time within an individual and across populations, current treatments are static in that they are not intended to co-evolve or persist along with the pathogen and disease; if a pathogen mutates in a way that undermines the therapeutic attack, then the therapeutic becomes less effective or useless. Thus, static therapeutics often cannot control dynamic pathogens and diseases that evolve, persist, and spread through populations, and therapeutics must be continuously re-formulated and re-developed to attempt to keep pace with emerging strains and disease variants (e.g., influenza and the need for annual vaccination). Many of these non-adaptive therapies must be administered across populations for lifelong duration. The misalignment between dynamic disease states and static therapeutics imposes a major economic burden and helps to explain why evolving diseases remain largely difficult to control despite significant medical advances.

**Description**

The Biological Technologies Office (BTO) of the Defense Advanced Research Projects Agency (DARPA) is requesting information on revolutionary ideas to radically change the existing paradigm for treating and controlling a variety of dynamic diseases and biological threats, such as rapidly mutating viruses, drug-resistant bacteria and evolving chronic pathologies and conditions. DARPA requests information on new research approaches and novel therapeutic paradigms targeting the mutating and evolving character of pathogens and/or the dynamic host response. Of particular interest are novel therapeutics engineered for “auto-adaptive” release, pathogen- or disease-triggered expression/activation, and/ or therapeutics that control disease spread by self-transmitting within an individual and through populations (e.g., through drug persistence, and person-to-person transmissibility). These adaptive therapies may address not only fast-evolving dynamic pathogens and diseases, but also individual variability of disease and host response by co-evolving control mechanisms, or adaptive targeted delivery and/or release based on individual dynamics (e.g., through optimal timing, continuous monitoring of host response while modulating immune components, or co-evolving control agents).

Examples of self-adapting therapeutics may include, but are not limited to, drugs or agents that: 1. dynamically change to compete with rapidly mutating viruses; 2. adapt to bacterial life cycle changes (multidrug resistant); 3. remodel host tissues in response to infection; 4. modify or re-populate a disease-enhancing or controlling microbiome; 5. dynamically control the type, magnitude and/or timing of the immune response, thereby

mitigating host damage while maintaining therapeutic effect; 6. enable controlled release of therapeutics in response to altered metabolite profiles, aberrant cell cycling or other abnormal cell process.

Responses to this RFI should focus on a particular indication (i.e., specific dynamic etiologic agent or exacerbating host response) but should show how the approach may generalize the therapeutic approach for a broad type of pathogens. Examples of indications may include (but are not limited to): 1. rapidly mutating RNA viruses (e.g., influenza, HIV); 2. multidrug-resistant bacteria (e.g., CRE, Acinetobacter); 3. rapidly spreading endemic pathogens difficult to control at the population level (e.g., malaria); 4. vector-borne and parasitic diseases for which vaccine and drug development have been challenging (e.g., dengue, Lyme, West Nile); 5. highly heterogeneous, immune-evading diseases (e.g., cancer); 6. chronic or latent infections (e.g., Epstein-Barr virus, tuberculosis); 7. chronic non-infectious conditions (e.g., asthma, cardiovascular disease, autoimmune disorders).

In addition, responses to this RFI should include approaches to address safety and efficacy of the proposed therapeutic paradigms related to (but not limited to): 1. *in vivo* and/or *in vitro* models of disease evolution and therapeutic effect; 2. methodologies to monitor and assess real time host-disease dynamics; 3. predictive mathematical models of pathogen-therapy co-evolution at the cellular, organism, and population levels; and 4. models of host-microbiome and microbiome-disease dynamic interactions. If addressing the particular indication of vector-borne and parasitic diseases, approaches to extend therapeutic persistence and adaptation beyond host-pathogen dynamics, including drug interactions with vectors (e.g., mosquito) and hosts other than humans should be addressed.

Submissions to this RFI should be in the form of white papers proposing novel adaptive therapeutic approaches and outlining the necessary technical areas of research needed to develop them. This RFI is not a request for proposals (RFP) and it is not associated with any existing Broad Agency Announcement (BAA). Responses to this RFI will not be associated with abstracts or full proposals submitted to any BAAs announced in the future.

**SUBMISSION FORMAT**

White papers should adhere to the following formatting and outline instructions:

a) A one-page cover sheet that identifies the title, organization, respondent's points of contact (names, addresses, phone number, and email addresses);
b) Up to 3 presentation slides summarizing key aspects of the response;
c) Microsoft Word file, 12-point font, not to exceed three pages, describing the response, to include:
    - Technical Concept: address the novel idea, briefly describing the technical approach, and the perceived impact on treatment and prophylaxis

strategies. A complete analysis with exhaustive technical details of the proposed approach is not required.

- Technical Research Focus: summarize the technical research breakthroughs needed for the technology to reach its potential, and a description of the in vitro or animal studies needed to validate the approach.

**SUBMISSION INSTRUCTIONS**

Responses to this RFI should be submitted via email to DARPA-SN-15-54@darpa.mil, no later than 4:00 PM ET, August 25, 2015. Please include "ADAPT RFI" in the subject line in all correspondence.

**DISCLAIMER**

This is an RFI issued solely for information gathering purposes; this RFI does not constitute a formal solicitation for proposals or abstracts. In accordance with FAR 15.201(e), responses to this notice are not offers and cannot be accepted by the Government to form a binding contract. DARPA will not provide reimbursement for costs incurred in responding to this RFI. Respondents are advised that DARPA is under no obligation to acknowledge receipt of the information received or provide feedback to respondents with respect to any information submitted under this RFI. Submission of a white paper is voluntary and is not required to propose to any subsequent solicitations on this topic.

**No classified information shall be included in the RFI response.** White paper submissions containing proprietary data should have the cover page and each page containing proprietary data clearly marked as containing "proprietary" data. It is the respondent's responsibility to clearly define to the Government what is considered proprietary data.

**POINT OF CONTACT**

Dr. Jim Gimlett, Program Manager, DARPA. All inquiries on this RFI must be submitted to DARPA-SN-15-54@darpa.mil. No telephone inquiries will be accepted.