NIH Countermeasures Against Chemical Threats (CounterACT) program

Therapeutics Discovery and Early-Stage Development Trans-NIH Funding Opportunities

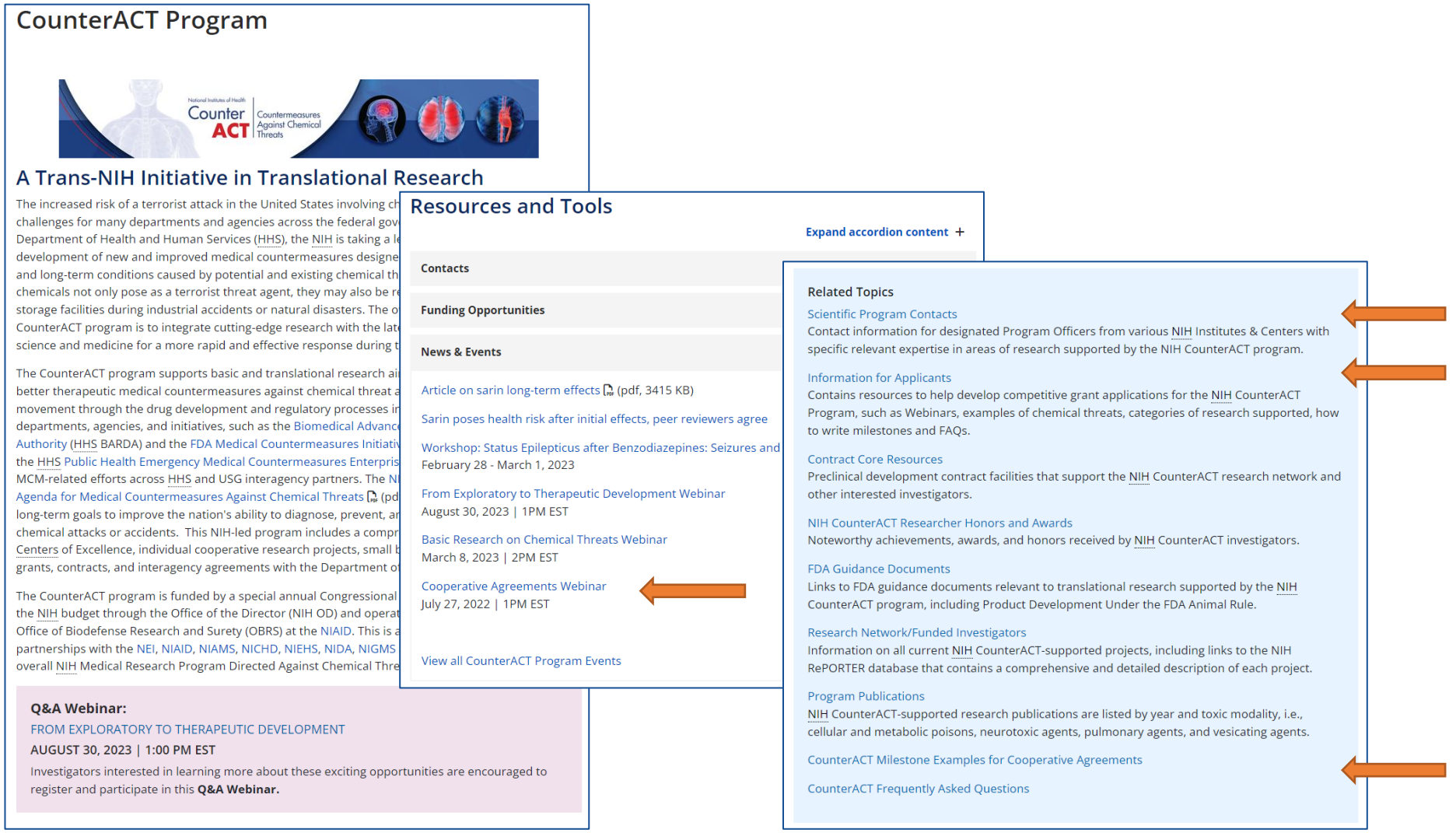
Informational Webinar

August 30, 2023

Goals of webinar

1. Description of the Research Program
2. Trans NIH NOFOs (R21 and UG3/UH3)
3. Tips for Applicants

Previous webinars are available for viewing



https://www.ninds.nih.gov/current-research/trans-agency-activities/counteract-program

The Mission

To understand fundamental mechanisms of toxicity caused by chemical threat agents and the application of this knowledge to develop promising therapeutics for reducing mortality and morbidity caused by these agents

Overall Goals

- Improve the nation's medical response capabilities
- Support cutting edge research to improve our knowledge base
- Develop optimized lead compounds for transition to advanced development

National Institutes of Health
CounterACT
Countermeasures Against Chemical Threats

The civilian chemical threat spectrum includes many chemical threats and routes of exposure

Chemical Warfare

- World War I and II: thousands of fatalities
- Iran-Iraq War (1980-88): thousands of fatalities
- Conflicts in the Middle East

Terrorism/Non-military malicious use

- Tokyo Subway Attacks (1995): thousands affected; 13 fatalities
- Tylenol and Excedrin poisonings (1980's): few fatalities
- Recreational drug adulteration
- Moscow theater hostage crisis

Industrial Accidents

- Occur Daily; thousands of injuries and fatalities annually
- Ohio train derailment
- Bhopal Union Carbide disaster (1984): 5,000 fatalities

General Poisonings

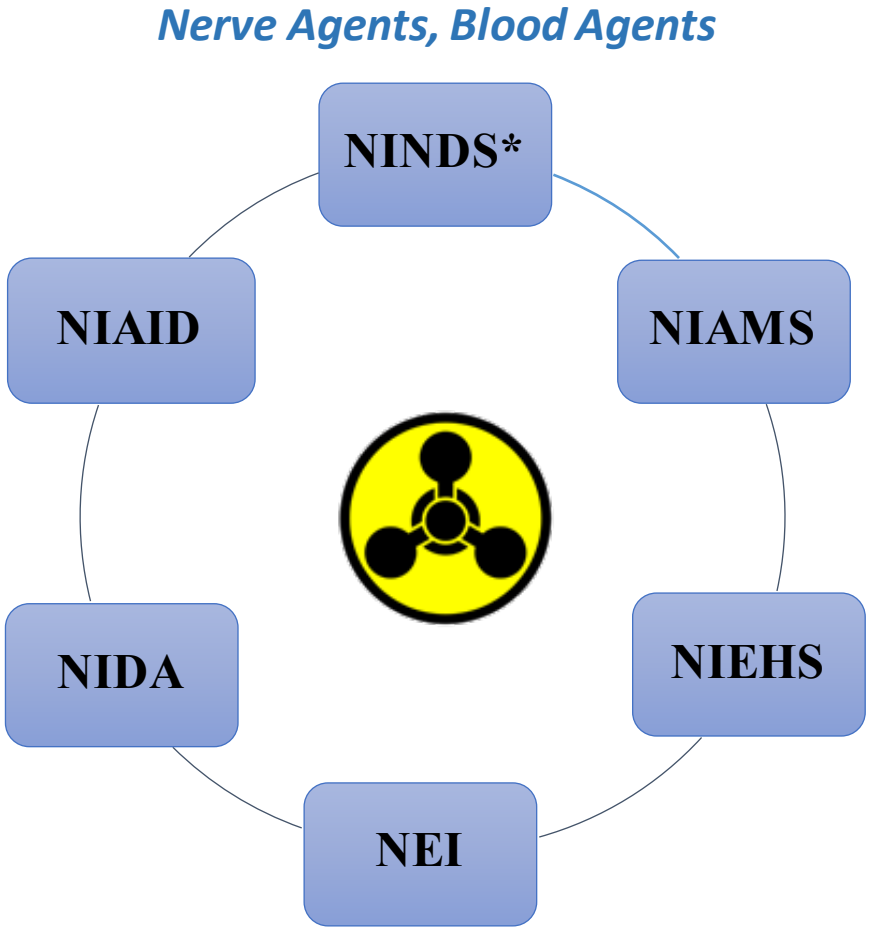
- Millions of calls to Poison Control Centers each year

CounterACT supports over 200 chemicals that are categorized in Toxidromes grouped by mechanism of action and toxic effects

Chemical Threat Toxidromes (some chemical threat examples)

- **Anticoagulants** (brodifacoum, bromadiolone)
- **Blood agents** (hydrogen cyanide, hydrogen sulfide)
- **Cholinergic warfare** (sarin, soman, VX)
- **Cholinergic pesticides** (parathion, chlorpyrifos, phorate, aldicarb)
- **Convulsant** (picrotoxin, TETS, strychnine)
- **Hemolytic/Metabolic** (arsenic trioxide, thallium sulfate, arsine)
- **Opioids** (fentanyl, diacetyl morphine)
- **Lower pulmonary** (chlorine, phosgene)
- **Upper pulmonary** (ammonia, sulfur dioxide, hydrogen fluoride)
- **Vesicants** (sulfur and nitrogen mustard, phosgene oxime)

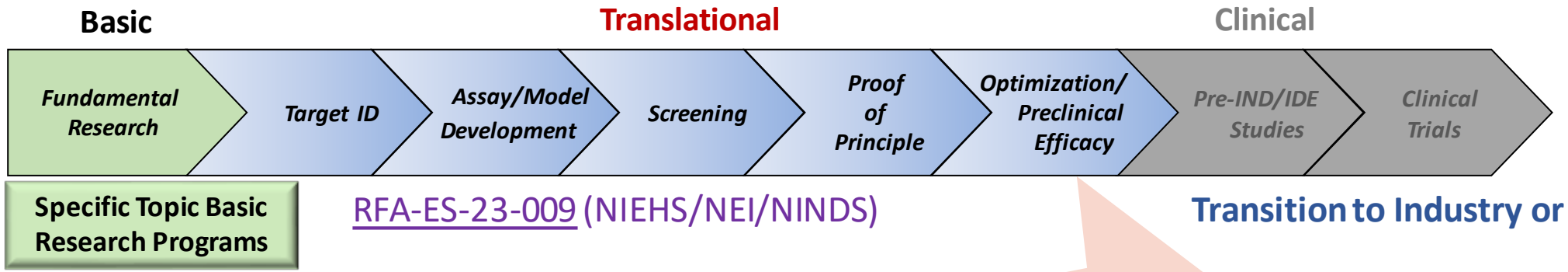
The NIH CounterACT program is a Trans-NIH Effort



- These ICs manage grants and contracts funded by NIH OD
- The NIH CounterACT Program also utilizes other expertise across the 27 NIH Institutes and Centers, e.g., NICHD, NLM, NHLBI.

* *Lead IC*

The CounterACT program has a suite of Notices of Funding Opportunity Announcements (NOFO) that span basic and translational research



National Institutes of Health
Turning Discovery Into Health

https://www.ninds.nih.gov/current-research/trans-agency-activities/counteract-program

National Institutes of Health
CounterACT
Countermeasures Against Chemical Threats

Which individual research project NOFO is right for me?

- I don't know which molecular target or mechanisms to study with this chemical threat.
- I have no candidates for drug development.
- I am new to the field of chemical countermeasures research.

= Basic Research Topic R01/R34s

- I have no assays or animal models.
- I have a candidate, but no preliminary data to support a competitive application to the CounterACT program.

= Exploratory/Developmental R21 (PAR-23-139)

- I know the target and mechanism but it has not been confirmed.
- I have "hits" or initial lead candidate(s) that will serve as a starting point for optimization/ drug development, but I do not have data on proof of concept in vivo efficacy.
- I have "freedom to operate", no obvious IP issues concerning drug development

= UG3/UH3 (PAR-22-209)

Translational Exploratory/Developmental Research Projects (R21) PAR-23-139, Clinical Trial Not Allowed

Goal

- To generate preliminary preclinical, screening, and/or efficacy data that would facilitate the development of competitive applications for more extensive support from the NIH CounterACT cooperative agreement programs or other related initiatives.

- This R21 NOFO only accepts applications proposing exploratory translational research directly related to the preclinical development of novel treatment strategies/approaches that address adverse health effects after exposure to chemical threats.

Scope (includes but not limited to)

- Creation and validation of clinically relevant *in vivo* or *in vitro* models of post-exposure lethality (serious near and long-term chronic morbidities)
- Evaluation of new combination treatment strategies and development of new agents to enhance the effectiveness of standard-of-care therapies
- Artificial Intelligence/Machine Learning models for the purpose of investigating/discovering novel MCM strategies to modulate chemical toxicity
- Discovery of candidate therapeutics using primary and secondary screening
- Preclinical development of new molecular targeting agents, biologics, or novel strategies based on specific changes in signaling pathways and proteins/genes expression during the post-exposure injury process
- Proposals seeking to repurpose/expand indications of already approved/authorized products

R21, PAR-23-139; Non-responsive applications will not be reviewed

- Applications that propose research on chemical threats that are not on the current Department of Homeland Security (DHS) List of Chemicals of Concern (CoC). Check with us!
- Applications that propose therapeutics unlikely to be amenable during or after a mass casualty scenario. This includes therapeutics that must be administered prophylactically or within the first 15-30 minutes of exposure. For ultra-potent synthetic opioids only, the administration of therapeutic(s) may be as short as 5 minutes post-exposure. Check with us!
- Applications addressing health outcomes after chronic chemical exposure, i.e., this NOFO only supports research on health effects after a single acute exposure event
- Applications proposing to develop environmental decontamination and/or analytical detection technologies and strategies
- Applications that only include basic research on mechanisms of toxicity from acute exposures of chemical threats

Translational Exploratory/Developmental Research Projects (R21) PAR-23-139, Clinical Trial Not Allowed

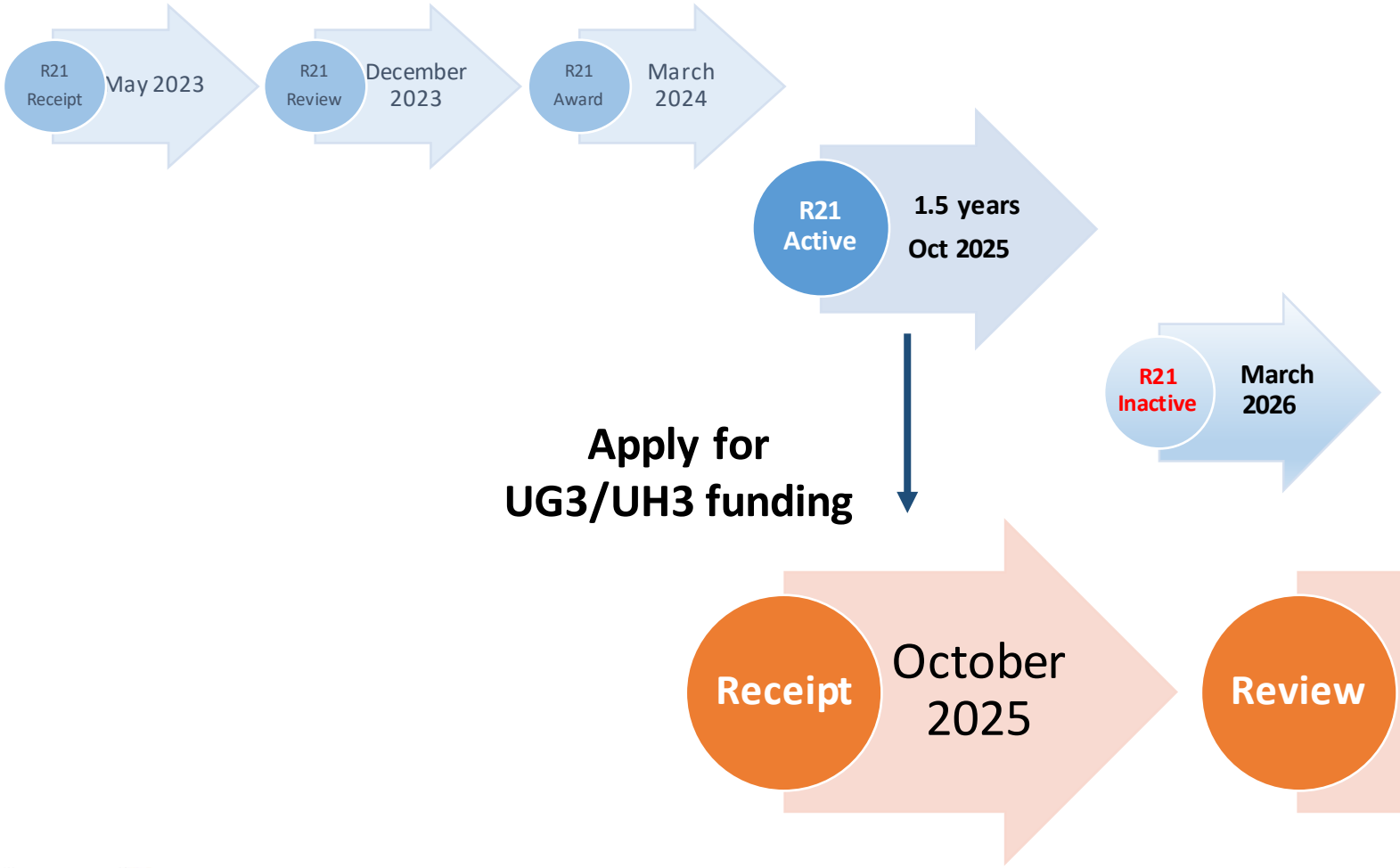
Budget: Direct costs may not exceed $275,000/ project period

- No more than $200,000 may be requested in any single year

Project Period: May not exceed 2 years, no renewals

Next receipt date is May 30, 2024!

Considerations for CounterACT Funding Cycles



An important consideration for research progress –

R21 projects should generate preliminary preclinical, screening, and/or efficacy data that would facilitate the development of competitive applications for more extensive support.

Plan your R21 so that the generated data will meet or exceed UG3/UH3 entry criteria.

CounterACT Therapeutics Discovery and Early-Stage Development (UG3/UH3) PAR-22-209, Clinical Trial Not Allowed

Goal

Early-stage development of therapeutics to mitigate the adverse health effects of toxic chemical exposure. Projects should deliver a well-characterized therapeutic at the end of the funding period.

- A well-characterized therapeutic will have demonstrated affinity, potency, target selectivity and engagement, *in vivo* efficacy, ADME/Tox in an animal model that is predictive of the human condition during or shortly after a mass casualty event, including timing and route of administration.

Scope

Research that is clearly relevant to the development of MCMs that will enhance national medical response capabilities during or after a large-scale chemical emergency. The overall scope of this solicitation includes validation of therapeutic targets through preclinical characterization of lead compounds.

CounterACT Therapeutics Discovery and Early-Stage Development (UG3/UH3) PAR-22-209, Clinical Trial Not Allowed

Entry Criteria

Rigorous data supporting hypothesis, Initial lead compounds and assays (in hand) that enable down-selection to lead candidate, Freedom to operate

Budget

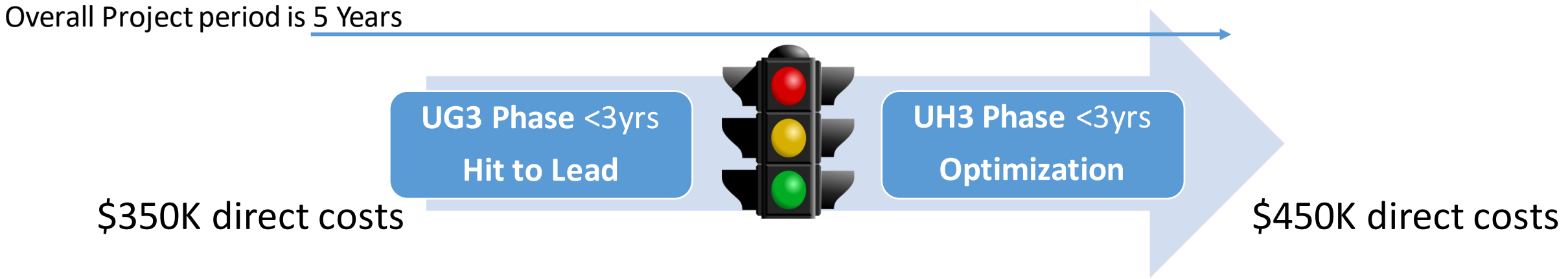
Applicants may request up to $350,000 direct costs annually for the UG3 phase and up to $450,000 direct costs for the UH3 phase per year

Overall Project Period

May not exceed 5 years, neither phase can exceed 3 years, no renewals

Next receipt date is October 17, 2023

The UG3/UH3 Mechanism is a milestone gated mechanism with distinct research areas and programmatic oversight



Overall Application should be a single application with a research plan consisting of two phases.

- **Specific Aims:** Provide the overall goals for the entire application and indicate separately Specific Aims to be accomplished in the UG3 phase and in the UH3 phase.
- **Milestones:** The application must include well-defined annual milestones and timelines (e.g., a Gannt Chart) for assessing progress in both the UG3 and UH3 phases, including *specific milestones* for transitioning from the UG3 phase to the UH3 phase.

Transition to the UH3 phase does not automatically follow completion of the UG3 phase, there is an Administrative and Scientific Review.

Different activities should be conducted in the UG3 and UH3 phases

UG3 Phase Activities

Hit to lead activities that enable down-selection from candidate therapeutics to a single lead compound.

- Validate target/pathway engagement
- SAR/ structure refinement to optimize hits/leads
- Development and utilization of relevant post-exposure animal models to demonstrate preliminary proof-of-concept efficacy
- Preliminary safety and PD/PK properties of the candidate therapeutic
- Preparatory activities for the UH3 Phase

Transition Milestone

UH3 Phase Activities

Optimization activities that enable characterization of the lead candidate for further development

- Specificity, affinity, potency, target selectivity/uptake/engagement, post-exposure *in vivo* efficacy, ADME/Tox
- Demonstration of therapeutic efficacy in relevant animal models predictive of the human condition in a post-exposure event
- *In vivo* dose-ranging and efficacy (non-GLP) studies against the chemical threat consistent with the product's intended therapeutic use regimen
- Optimization of formulations and delivery systems that can be effectively employed in a mass-casualty situation
- Draft Preliminary Target Product Profile

Milestones are clear and quantitative outcomes that set go/ no-go criteria for continuing the project

Bad

01 Milestone #1: Test if drug X is efficacious in mice.

Criteria for success: **Completion of lethality tests** in mice exposed to cyanide by the end of year 1.

Rationale: Lethality is an acceptable endpoint for cyanide toxicity.

Good

01 Milestone #1: Demonstrate efficacy in reducing lethality when drug X is administered at 20 minutes after cyanide challenge.

Criteria for success: **Reduction in lethality in mice by 50%** when drug X is administered (IM) 20 minutes following an acute LCt_{50} dose of HCN via inhalation. Efficacy is evaluated at 24 h after exposure.

Rationale: Lethality is an acceptable endpoint for cyanide toxicity. A reduction in lethality 50% is a threshold effect that represents a starting point for subsequent studies with higher doses of the candidate compound to increase efficacy.

For more on milestones, see CounterACT Milestone Examples

UG3/UH3, PAR-22-209; Non-responsive applications will not be reviewed

- Applications that propose research on chemical threats that are not on the current Department of Homeland Security (DHS) List of Chemicals of Concern.
- Applications that propose therapeutics unlikely to be amenable during or after a mass casualty scenario.
- Applications addressing health outcomes after chronic chemical exposure, i.e., this NOFO only supports research on health effects after a single acute exposure event.
- Applications lacking quantitative, go/no-go milestones and clear delineation of activities relevant to the UG3 or UH3 phase of the project.
- Proposals that include advanced development activities.
- Applications that propose assay development for discovery of novel therapeutic compounds.
- Applications that propose screening to identify hit compounds.
- Applications with a primary focus to develop de novo animal models.
- Applications with a primary focus to develop diagnostics and/or devices.

There are some important considerations to address when preparing your application

NIH-specific

- **Enhancing Reproducibility through Rigor and Transparency** (NOT-OD-15-103),
- **Implementing Rigor and Transparency** (NOT-OD-16-011), (NOT-OD-18-228)

  - The rigor of the prior research
  - Rigorous experimental design
    - include power calculations in the approach
  - Consideration of sex and other relevant biological variables
  - Authentication of key biological and/or chemical resources

- **Do not use the Vertebrate Animals or Facilities sections for additional experimental details, any type of analyses, rationale, or power calculations**

Additional considerations when preparing an application for the NIH CounterACT program

CounterACT-specific

Practicality in real-world civilian mass casualty situations

- Product should have utility for emergencies involving acute chemical exposures where medical intervention is required immediately in the field or in-hospital (more than 15-30 minutes post-exposure)
- Prophylactic therapeutic approaches that are administered before chemical threat exposure, are considered non-responsive to this FOA, and will not be reviewed as they to do not have practical utility during a mass casualty event

Drugs already approved by the FDA (repurposing) are welcome!

Additional considerations when preparing an application for the NIH CounterACT program

CounterACT-specific

Research Strategy

- Include the structure of your lead compound when possible. If not, provide an explanation.
- Include your letters of support (collaborators, appropriate biosafety committee, etc.,).
- Address biohazards and facilities needed for restricted chemicals (warfare agents).

Intellectual Property (IP) Strategy (1 page)

- Work closely with your institutional Technology Transfer (or Industry Relations) Office.
- Applicants should have “freedom to operate”. Describe any known constraints to development and eventual commercialization of the therapeutic and how these issues could be addressed.
- When applicable, discuss details of patents pertinent to the therapy being developed under this application.

Further application considerations

- Scientific feasibility
  - preliminary data and the literature should support the hypotheses and proposed studies
- Present sufficient details to evaluate the approach
- Ensure the work meets the goals of the project
- If needed, be sure to address interdependence of aims
- Discuss alternative approaches to research strategies presented
- Describe how the team will communicate, especially MPI plans

NIH CounterACT program is a trans-NIH effort with designated scientific program contacts.

Center for Scientific Review (CSR) - preparation of application, required docs, details concerning review process
Jodie Fleming, PhD; Scientific Review Officer; jodie.fleming@nih.gov

National Institute of Neurological Disorders and Stroke (Lead IC) – nerve agents, anticoagulants, and blood agents
Shardell Spriggs, PhD; NIH CounterACT Program; shardell.spriggs@nih.gov

National Institute of Arthritis and Musculoskeletal and Skin Diseases – vesicants
Alexey Belkin, PhD; alexey.belkin@nih.gov

National Institute of Environmental Health Sciences – pulmonary agents
Srikanth Nadadur, PhD; nadadurs@niehs.nih.gov

National Eye Institute – ocular toxicity
Houmam Araj, PhD; arajh@nei.nih.gov

National Institute on Drug Abuse – ultra-potent synthetic opioids
Kiran Vemuri, PhD; kiran.vemuri@nih.gov

Applicants are strongly encouraged to contact NIH Scientific Program contacts to determine if their proposed threat agent(s) is of interest to the NIH CounterACT Program.