NIH Countermeasures Against Chemical Threats (CounterACT) Therapeutics Discovery and Early-Stage Development (UG3/UH3 Clinical Trial Not Allowed)

PAR-22-209
Funding Opportunity Announcement Informational Webinar

July 27, 2022

National Institutes of Health
Turning Discovery Into Health

National Institutes of Health
CounterACT
Countermeasures Against Chemical Threats

Goals of Webinar

1. Description of the Research Program
2. PAR-22-209, UG3/UH3 Mechanism
3. Tips for Applicants

CounterACT Mission and Goals

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

The civilian chemical threat spectrum includes many chemical threats of research interest.

- Traditional Chemical Warfare Agents such as nerve “gases”
- Toxic Industrial Chemicals
- Toxic Agricultural Chemicals such as insecticides and rodenticides
- Pharmaceutical-based agents
- Other chemicals

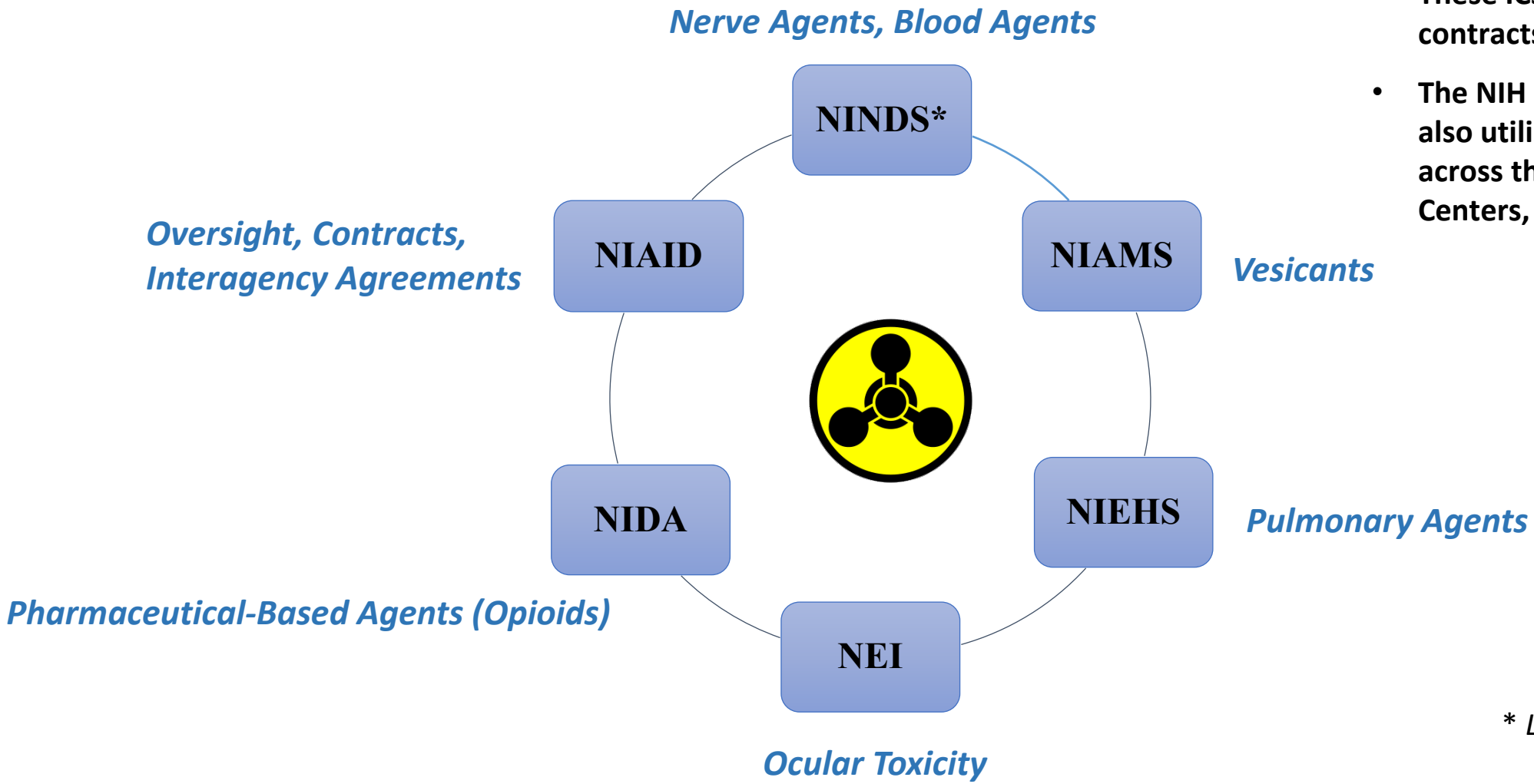
Contact NIH Scientific Program contacts to confirm your chemical is eligible.

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)

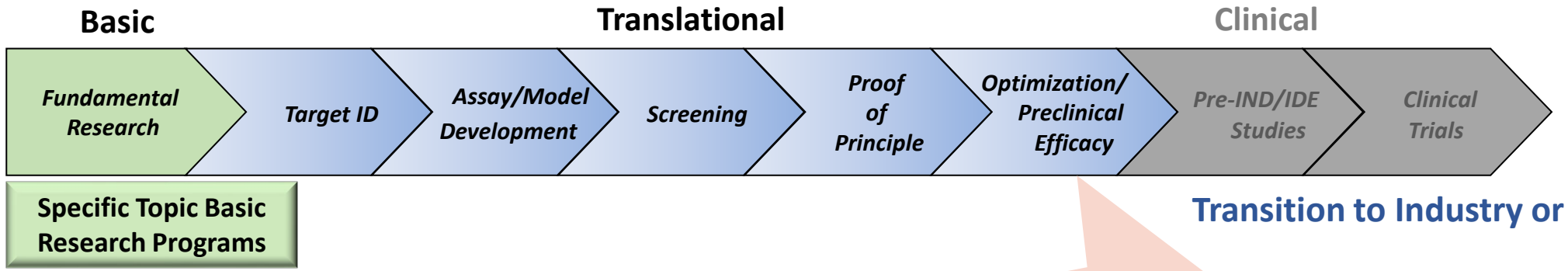
The NIH CounterACT program is a Trans-NIH Effort



- 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 Funding Opportunity Announcements that span basic and translational research



Hit to Lead Therapeutic Development Research
(UG3/UH3) PAR 22-209

Exploratory/ Developmental Research
(R21) PAR 20-253

Basic Research
(R01/R34)
PAS-21-245
RFA-ES-21-006

Which individual research project FOA 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-20-253)

- 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)

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 that enable down-selection to lead candidate (in hand), 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

First receipt date is October 17, 2022

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

Non-responsive applications will not be reviewed.

- Chemical threat must be on the current DHS List of Chemicals of Concern
- Therapeutics must be amenable during or after a mass casualty scenario.
- No chronic chemical exposure models. We only support research on health effects after a single acute exposure event.
- No quantitative, go/no-go milestones or clear delineation of UG3/UH3 phase activities
- No advanced development activities such as 1) GLP IND-enabling safety studies; 2) Pivotal efficacy studies in animals; 3) cGMP production; 4) Human clinical trials.
- 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.
- Therapeutics only for specific vulnerable subpopulations.

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)

  - Rigorous experimental design,
  - consideration of sex and other relevant biological variables,
  - authentication of key biological and/or chemical resources,
  - the rigor of the prior research

- **Do not use the Vertebrate Animals section for experimental details**

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**

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

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

National Institute of Arthritis and Musculoskeletal and Skin Diseases – vesicants
Hung Tseng, PhD; tsengh@mail.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 – pharmaceutical-based agents (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.