National Institutes of Health
Counter ACT
Countermeasures Against Chemical Threats

Basic Research on Chemical Threats that Affect the Nervous System

(R01 Clinical Trial Not Allowed)

PAR-23-027

Funding Opportunity Announcement Informational Webinar

March 8, 2023

NIH National Institutes of Health
Turning Discovery Into Health

Goals of Webinar

1. Description of the Research Program
2. PAR-23-027, R01 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

Exposure to Chemical Threats

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

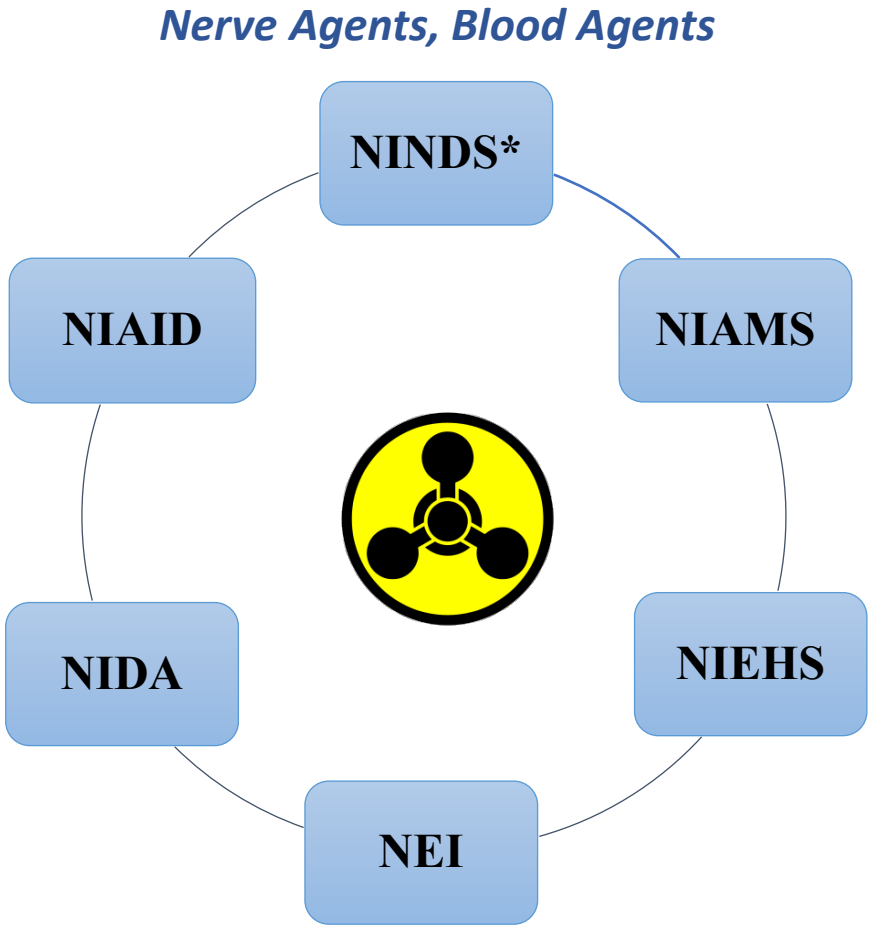
Industrial Accidents

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

General Poisonings

- Million of calls to Poison Control Centers each year

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.

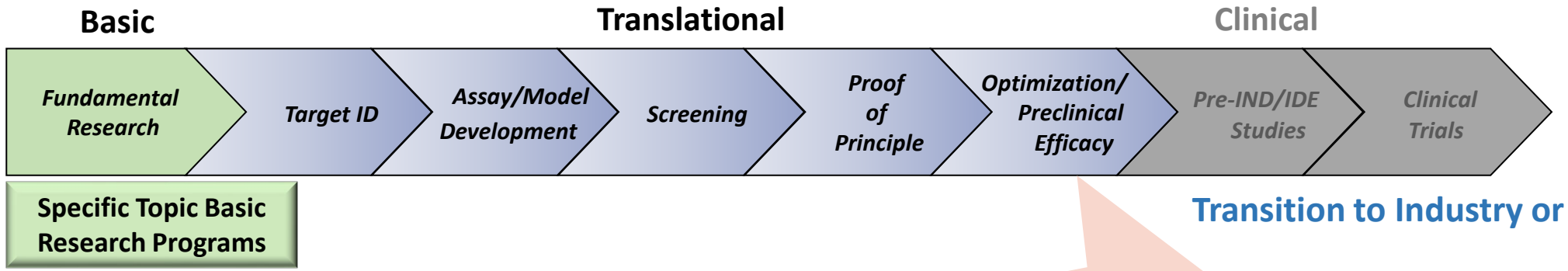
* *Lead IC*

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 CounterACT program has a suite of Funding Opportunities that span basic and translational research



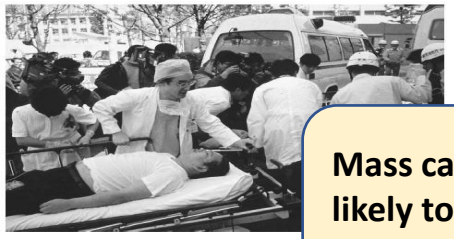
Hit to Lead Therapeutic Development Research
(UG3/UH3) PAR 22-209

Exploratory/ Developmental Research
(R21) PAR 20-253

Basic Research
(R01/R34) **PAR-23-027**
PAS-21-245
RFA-ES-21-006
RFA-DA-23-036

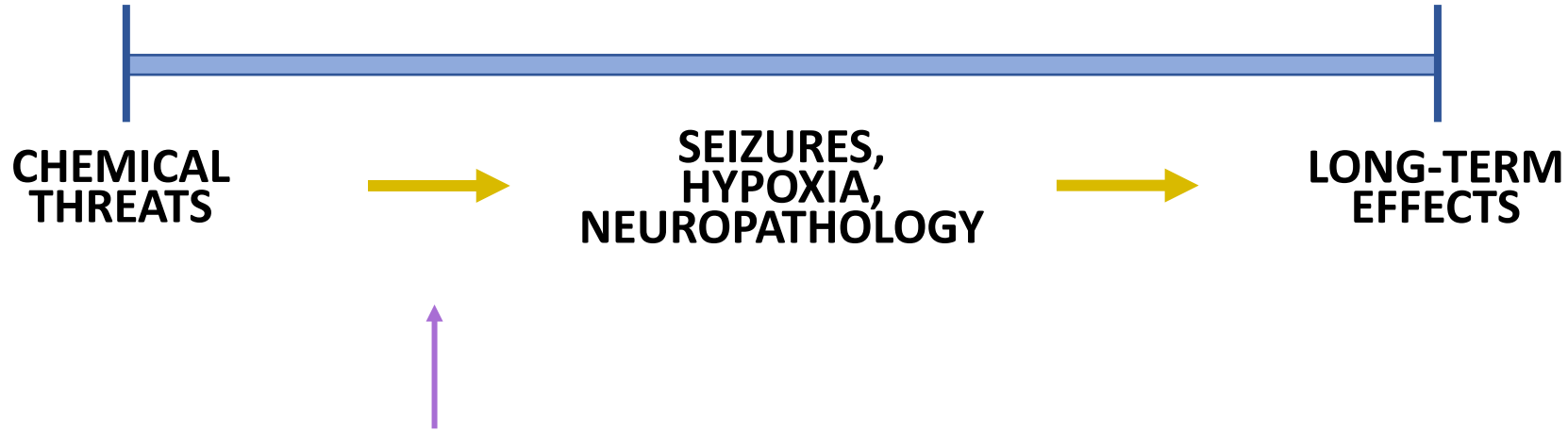
http://www.ninds.nih.gov/CounterACT

The CounterACT program is interested in the mechanistic basis of toxicity related to acute exposures.



Mass casualties: Treatments likely to occur 30 - 120 minutes after exposures.

There is a spectrum of interests targeted by this funding opportunity, including short-term toxicity through long-term effects.



CounterACT Basic Research on Chemical Threats that Affect the Nervous System (R01 Clinical Trial Not Allowed) PAR-23-027

Goal

Projects are expected to generate data that elucidate mechanisms of toxicity of chemical threats, new manifestations of toxic exposures, and potential targets for therapeutic development.

Scope

Basic research relevant to understanding the mechanism(s) of toxicity and pathology of chemical warfare agents, toxic industrial chemicals, and pesticides that have primary or secondary effects on the nervous system, including long-term effects of acute exposures.

Research topic examples

- Identification of molecular mechanisms of **acute toxicity** to chemical agents and identification of relevant biological markers and/or targets for therapeutic development
- Elucidation of the mechanistic basis of **long-term effects of acute exposures** to chemical agents
- Development of *in silico*, *in vitro*, and *in vivo* models to elucidate known and unknown mechanistic pathways of toxicity
- Using *in vivo* models for natural history studies of toxicity of chemical agents
- Identification of the mechanistic linkage between signaling molecules and their biological targets and deciphering their functional relationships and physiological roles to better understand toxicity of acute exposures from chemical agents
- Mechanisms of toxicity that are not addressed by the current standard of care for CoCs, including mechanisms or targets that improve refractory status epilepticus (SE) and post SE neuropathology after acute exposure to chemical threats
- Mechanisms of toxicity that cause neurodegeneration or alter neurodevelopment, the brain environment, the blood-brain barrier, neurogenetics, neural excitability, or neural circuitry.
- Applications that use more than one chemical threat within a toxidrome are encouraged.

Not limited to just these research activities

CounterACT Basic Research on Chemical Threats that Affect the Nervous System (R01 Clinical Trial Not Allowed) PAR-23-027

Entry Criteria

Rigorous data supporting the hypothesis that the putative mechanistic pathway(s) are relevant to chemical toxicity

Budget

Applicants may request up to $300,000 direct costs annually.

Overall Project Period

May not exceed 3 years

Next receipt dates: May 30, 2023
October 17, 2023

Non-responsive applications will not be reviewed

- Chemical threat must be on the current DHS List of Chemicals of Concern
- Applications that propose to study CoC that have primary effects on the pulmonary, skin, or eye systems, or to study opioid-based chemical threats are non responsive
- No chronic chemical exposure models. We only support research on health effects after a single acute exposure event
- Clinical trials will not be considered
- **Studies on the creation and validation of candidate therapeutics are non-responsive**

There are some important considerations to address when preparing your application

- **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**
- **Include your letters of support (collaborators, appropriate biosafety committee, etc.)**
- **Address biohazards and facilities needed for restricted chemicals (warfare agents)**

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**
- **Early-stage Investigator (ESI) status**

NIH CounterACT Program Contacts for PAR-23-027

Shardell Spriggs, PhD; shardell.spriggs@nih.gov

Neel Dhruv, PhD; neel.dhruv@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.

Additional programmatic contacts can be found on our website.

http://www.ninds.nih.gov/CounterACT

Research Supplements to Promote Diversity in Health-Related Research, PA-21-071