

CounterACT Neurotherapeutics Screening Program

The NIH NIAID Chemical Countermeasures Research Program (CCRP) offers established animal screening models to accelerate research and development of novel medical countermeasures (MCMs) against organophosphorus (OP) chemical threats that target the central nervous system. These models are available through the CounterACT Neurotherapeutics Screening (CNS) program to support translational studies evaluating the potential *in vivo* efficacy of investigational MCMs. This NIH-supported screening program is conducted at the U.S. Army Medical Research Institute of Chemical Defense (USAMRICD). Studies are performed at *no cost* to the investigator or supplier.

The purpose of the CNS program is to provide applicants with pre-application proof-of-principle efficacy data in support of potential follow-on research efforts such as an application to the NIH-wide Countermeasures Against Chemical Threats (CounterACT) grant program. The proposed studies must not overlap with, but may be conducted in concert with, studies performed by other CCRP efficacy or preclinical research support services. The CNS program does *not* replace the need to establish direct collaborations with laboratories certified to work with restricted chemical agents.

Participants will retain custody of and have primary rights to the data developed, subject to government rights of access consistent with current HHS, U.S. Public Health Service, and NIH policies. All information provided to the NIH contractor will be treated as confidential.

Program Description and Goal

OP-induced seizures result from overstimulation of susceptible brain circuits by abnormally high levels of the excitatory neurotransmitter acetylcholine, which rapidly builds up after inhibition of the enzyme acetylcholinesterase by an OP nerve agent. These seizures rapidly progress to a condition known as *status epilepticus* (SE), a medical emergency only treatable with a subset of known anticonvulsant drugs.

The current MCM approach to treat OP-induced seizures includes administration of a benzodiazepine-based anticonvulsant such as midazolam along with atropine

Interested in developing MCMs against chemical threats that target the nervous system?

CNS
offers established animal screening models.



and pralidoxime chloride. Although this treatment is efficacious to an extent, overall improvements in both mortality and morbidity outcomes are highly desired. The goal of the CNS program is to identify novel neurotherapeutics that may be administered together with approved treatments in a civilian first-responder setting to more effectively suppress SE activity and/or mitigate neuropathology after OP exposure.

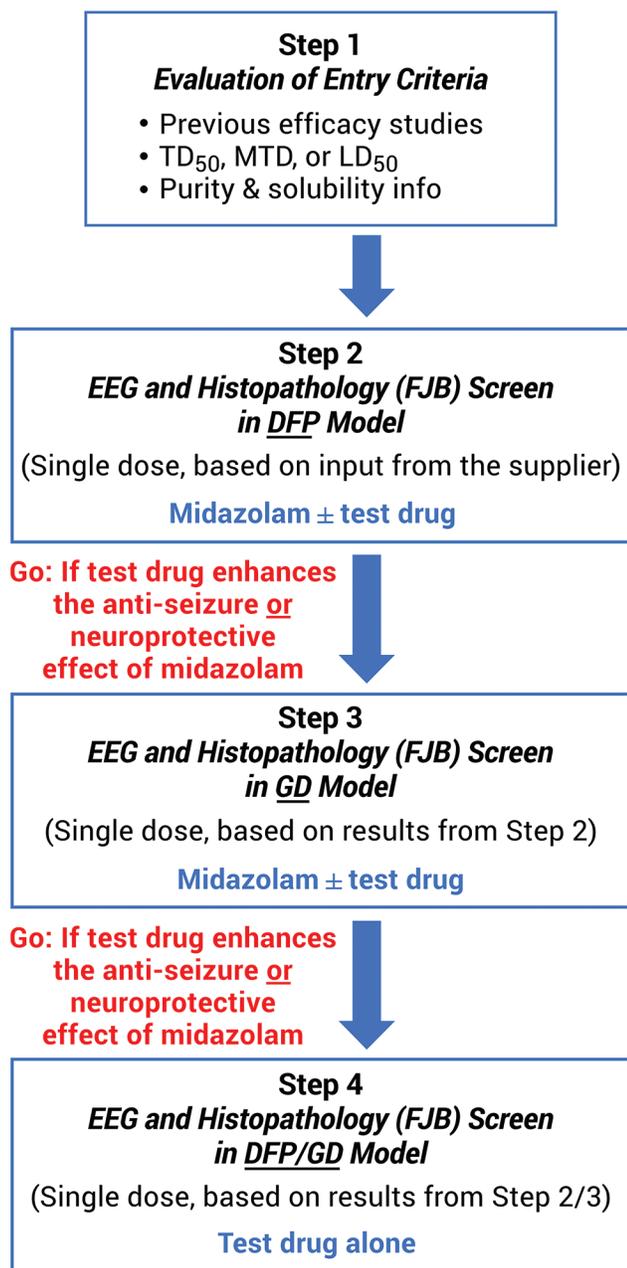
Screening Models

The CNS program employs the following *in vivo* screening models:

- Diisopropylfluorophosphate (DFP)-induced electrographic SE model in rats
- Soman (GD)-induced electrographic SE model in rats

Both screening models use 24-hour electroencephalographic (EEG) recordings to determine the efficacy of investigational compounds in suppressing electrographic SE and histopathology with Fluoro-Jade B (FJB) staining to evaluate the potential neuroprotective effects of the compounds. A final report will be delivered to the investigator or supplier at the end of the study.





Eligibility Criteria

In general, the CNS program is available to all investigators with promising MCMs responsive to the mission of the CCRP. NIH will accept applications from individual principal investigators (PIs) from academic institutions, government laboratories, and companies.

PIs from foreign institutions and non-U.S. components of U.S. organizations are *not* eligible to apply. PIs may consult with NIH to determine eligibility.

The supplier of the test compound must provide documentation regarding compound toxicity, solubility, purity, and previous *in vivo* efficacy studies. Solubility information determines the best vehicle and route of administration. Toxicity data—such as the median toxic dose 50 (TD₅₀), maximum tolerated dose (MTD), or median lethal dose 50 (LD₅₀)—and data from previous efficacy studies assist in identifying the range of doses for evaluation and aid in prioritizing the compounds to be tested.

The supplier must be able to provide a sufficient quantity of the compound with ≥ 95% purity (nuclear magnetic resonance [NMR] or high-performance liquid chromatography [HPLC] analysis) for evaluation in up to 60 animals based on the highest median effective dose (ED₅₀) of the previous efficacy studies.

Who To Contact

To learn more or to receive an application to enroll in the CNS program, please contact (preferably by email)

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Additional Information

NIH NIAID Chemical Countermeasures Research Program (CCRP)
<https://www.niaid.nih.gov/research/chemical-countermeasures-program>

NIH Countermeasures Against Chemical Threats Program (CounterACT)
<https://www.ninds.nih.gov/CounterACT>

U.S. Army Medical Research Institute of Chemical Defense (USAMRICD)
<https://usamricd.apgea.army.mil/>

