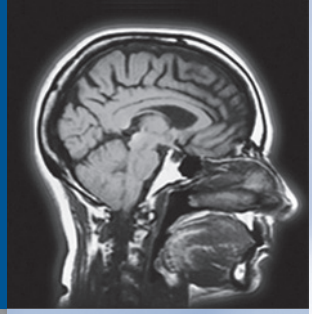
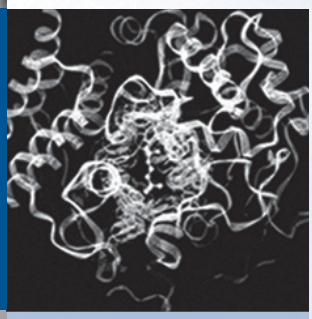
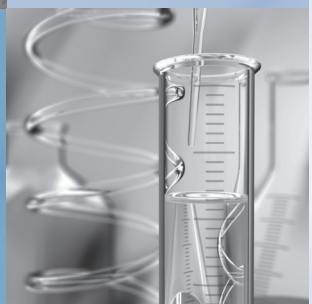


The NIH Medical Research Program Directed Against Chemical Threats

2011 Report on Research Progress and Future Directions





The NIH Medical Research Program Directed Against Chemical Threats

2011 Report on Research Progress and Future Directions

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

National Institute of Allergy and Infectious Diseases

FOREWORD

In August 2007, the National Institutes of Health (NIH) published the *National Strategic Plan and Research Agenda for Medical Countermeasures against Chemical Threats*. This plan defined a research strategy to (1) improve current approaches in the treatment of chemical casualties and (2) develop new countermeasures that could be used during and following an industrial accident or a chemical terrorist attack on civilian populations. The plan recognized that NIH-supported research should be conducted in parallel with the Department of Defense (DoD) because certain diagnostic tests and antidotes might be used in both military and civilian settings.

The Department of Health and Human Services (HHS) mandated that the National Institute of Allergy and Infectious Diseases (NIAID), part of the NIH, execute the strategic biodefense medical research plan against weapons of mass destruction (WMD) through collaborations with other NIH Institutes and Centers, other federal agencies, academia and industry. The ensuing program, the NIH Medical Research Program Directed Against Chemical Threats, is funded by a special Congressional supplement to the NIH budget, and is integrated closely with HHS medical product development efforts.

Impressive progress occurred in the three years after publication of the strategic plan and research agenda. This progress stems from convergence of several key elements, including sharing of expertise, information, and other resources from the NIH Institutes (ICs), such as the NIAID/National Institute of Neurological Disorders and Stroke (NINDS) effort to establish a national research program to develop medical products to counteract chemical threats. Interagency agreements with the U.S. Army and the establishment of a national academic and industrial research base dedicated to product development against chemical threats also facilitated important progress toward advancing the research effort. Interest in chemical research and medical product development has fostered new careers in scientific research and enabled NIH to recruit talented scientists, including Nobel Laureates. These researchers bring invaluable expertise to an area of research previously limited primarily to military laboratories, and help to raise the level of science in the entire field through their numerous publications in the top peer-reviewed scientific journals.

The NIH research focus on Medical Countermeasures against Chemical Threats is managed by the NIAID and NINDS and draws on research strengths of both NIH scientists and top NIH-grant recipients at research institutions and centers nationwide. For instance, through the Countermeasures Against Chemical Threats (CounterACT) Program, the NINDS and NIH partner ICs including the National Eye Institute (NEI), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Child Health and Human Development (NICHD), National Institute of Environmental Health Sciences (NIEHS), National Toxicology Program (NTP), National Library of Medicine (NLM), and National Institute of General Medical Sciences (NIGMS) established Research Centers of Excellence at academic, commercial and federal laboratories across the United States. These research centers focus on the health effects of hazardous chemicals and the underlying pathology. The NINDS also utilizes its existing scientific infrastructure and research expertise in the area of neurological disorders to advance research on chemical nerve agents and their effects. Other NIH Institutes, such as the NIEHS and the NIAMS, also manage research protocols. The CounterACT program leverages many NIH resources, such as the NTP and NLM, to fill data gaps in our knowledge of chemical agents, and the NIH Molecular Libraries Program to screen for new therapeutic targets. Finally, the NIH medical chemical program also draws upon the vast knowledge of chemical warfare agents and toxic chemicals acquired by the DoD and other Federal agencies, as well as industry. Workshops sponsored by the NIH engage leading authorities and experts from many federal agencies and academia in providing guidance to the overall program.

The chemicals of concern are based on assessments performed by the Department of Homeland Security (DHS) and progress reviews are conducted on a regular basis with the involvement of all appropriate federal agencies, including the NIH. Promising therapeutic compounds have now been identified, and studies have led to a deeper understanding of the causes of injury down to the molecular level. As this document shows, promising compounds discovered through the NIH CounterACT Program may prove to be useful in preventing or reducing morbidity and mortality from highly hazardous chemicals.

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TABLE OF CONTENTS

Foreword 4

Introduction 7

The Chemical Threat 7
Addressing the Chemical Threat through Research 7

Building The Research Infrastructure 8

Public Health Emergency Medical Countermeasures Enterprise 8
NIH Research and Development Program 8
The Chemical Countermeasures Research Community 10
The Trans-NIH CounterACT Program 10

Research Accomplishments Resulting From NIH Support of Chemical Threat Research 11

Progress Against Nerve Agents 11
Progress Against Metabolic Poisons 12
Progress Against Vesicants and Pulmonary Agents 13
Therapeutic Targets and Model Development 14

Looking To The Future 15

Appendices: 17

Table 1: Examples of Highly Hazardous Chemicals 17
Table 2: Key Workshops and Expert Panels on Chemical Threats and Medical Countermeasures 18
Table 3: 2006-2009 NIH CounterACT Funding Opportunity Announcements Soliciting Research Proposals 19
Table 4: 2006-2010 CounterACT Centers of Excellence and Primary Investigators 21
Table 5: Interagency Agreements (IAAs) 22
Figure 1: Overview Diagram of Trans-NIH CounterACT Program 24
Figure 2: CounterACT Medical Countermeasures and Technical Readiness Levels (TRLs) 25
Figure 3: Publications Resulting from CounterACT Investments 26

Introduction

The Chemical Threat

Historically, the Department of Defense (DoD) has been concerned about the use of chemical warfare agents (CWA), due to their potentially devastating effects on the battlefield. More recent events involving the expanded use of toxic chemicals as weapons has increased awareness of the effects such chemicals may have on both military and civilian populations. The procurement and preparation of chemical weapons is well-documented as a part of the doctrine of several radical terrorist groups. Additional evidence has been obtained that some terrorist groups are interested in staging chemical attacks on population centers, perhaps in combination with other weapons.

Highly toxic chemicals are now recognized as serious public health threats for a variety of reasons. First, unlike infectious diseases where incubation periods may allow for prophylactic measures to be instituted, chemical incidents can occur quickly with immediate generation of casualties. Second, many of the toxic industrial chemicals or their precursors may be easily procured or manufactured without detection. Third, it may difficult to ascertain if a chemical incident was accidental or deliberate, since chemical accidents can occur without warning or be associated with another disaster, such as an explosion. Fourth, extremist groups or individuals with limited scientific knowledge may be able to manufacture dangerous compounds without detection. Finally, the deliberate release of chemicals into the environment may increase the likelihood of injuries or death. This may be through deliberate contamination of food or water supplies or atmospheric release of volatile agents in enclosed spaces or poorly ventilated areas. Much attention has now been directed at how and where chemicals are manufactured, transported and stored in the U.S., but this will not prevent the desire of terrorists to cause destruction or disruption.

It is impractical to develop specific countermeasures against every dangerous chemical in the U.S. Hazardous acids, bases, and explosives alone represent chemical dangers for those working with such materials, and the importance of security and careful handling and storage cannot be overemphasized.

From a public health perspective where mass casualties might result from deliberate or accidental release of a chemical, high priority chemical threats include: (1) CWAs such as the "nerve gases" Sarin, VX, Soman, or their derivatives and Sulfur Mustard; (2) toxic industrial chemicals, such as Cyanide, Chlorine, and Phosgene; and (3) toxic agricultural chemicals, such as highly toxic insecticides (Parathion, Chlorpyrifos,and Disulfoton) and rodenticides (Sodium Fluoroacetate, Tetramethylenedisulfotetr amine(TETS), and Strychnine). These categories of chemicals exert their toxic effects through different mechanisms and on different organs of the body and physiological systems.

The Department of Homeland Security (DHS) Chemical Security Analysis Center has assisted in the analyses and prioritization of threats and has developed a "Chemical Terrorism Risk Assessment" (Appendix 1). Updates on risk based on modeling and other information are provided periodically. Response during and following events where chemicals are released are addressed under various emergency preparedness and response plans and include recommendations for employing specific medical interventions that could minimize the number and severity of casualties.

Addressing the Chemical Threat through Research

The DoD is a key element in the chemical countermeasures research effort since many military research and development priorities overlap with those of civilians, such as the needs of civilian first responders and health care providers in the event of a chemical agent

exposure. Even though DoD research has improved our understanding of how CWAs cause injury, research must continue as the list of chemical threats grows ever longer. The NIH research efforts initially focused on addressing the underlying injury processes resulting from chemical agents, including the toxicological effects of chemical compounds and their varying effects on the human body.

Advances in biotechnology, knowledge of host defenses, and human genomics has showed promise to counteract the threat of chemical compound exposures. These countermeasures would be important for protecting civilians, as many would not have access to personal protective equipment or pre-treatment medical countermeasures. In addition, these realizations directed attention towards development of immediate post-exposure interventions and the need to clearly understand how exposure to these compounds affects physiological, biochemical and immunological processes at all stages of life.

Due to these issues and the growing awareness that chemical agents pose a threat to public health, the Federal Government launched a new biodefense research effort with a goal to develop medical interventions to counteract the threat. To accomplish this goal, basic research initiatives were created to inspire advanced research and development for promising products. Successful completion of these initiatives would require participation by pharmaceutical companies, as well as HHS, specifically the Food and Drug Administration (FDA) and the Biomedical Advanced Research and Development Authority (BARDA). Federal programs such as Project Bioshield and the Strategic National Stockpile (SNS) continue to be very important in meeting this goal in that they provide market incentives to industry, particularly the pharmaceutical industry.

Building The Chemical Research Infrastructure

Public Health Emergency Medical Countermeasures Enterprise

Approximately five years ago, HHS established the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Strategy to address the public health threat from chemical, biological, radiological and nuclear (CBRN) agents. The PHEMCE Strategy established the goals and objectives that the HHS would employ to ensure that medical countermeasures are available in their critical hour of need. The implementation plan employed a “Four Pillars” approach, including: (1) identify and assess CBRN threats by conducting both material threat determinations and population threat assessments; (2) assess civilian medical and public health consequence assessments based on DHS scenarios of CBRN threats; (3) establish concept of operations for medical countermeasure requirements; and (4) identify and prioritize near-, mid-, and long-term research development and acquisition programs. The NIH effort to understand the pathology related to chemical exposure and develop specific medical treatments is a part of the overall PHEMCE Strategy, along with the focus on biological and radiological/nuclear research.

NIH Research and Development Programs

In support of the PHEMCE Implementation Plan, the NIH led the research and development of new medical countermeasures against CBRN threats. With regard to chemical threats, the NIH established a program to develop safer and more effective therapies and diagnostic technologies for treating victims of emergency incidents involving chemical threat agents as a part of an overall national biodefense research strategy. A series of workshops and expert panels have been held by the NIAID and NINDS to ascertain research gaps and develop priorities (Appendix 2).

In 2005, NIAID convened a NIAID Blue Ribbon panel to help define the parameters of a comprehensive biodefense research effort against chemical threats. The "*NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Chemical Threats*", published in 2007 (**http://www.niaid.nih.gov/topics/biodefenserelated/chemicalcountermeasures/Pages/defaultaspx**), resulted directly from the discussions and recommendations of this Panel. Recognizing the neurological effects of many of the highest priority chemicals, NIAID asked the National Institute of Neurological Disorders and Stroke (NINDS) to develop a research program on chemical threats that engaged academia and industry. NINDS had an active translational research program focused on neurological disorders that resembled symptoms caused by nerve agents.

To complement the expertise in neurological effects, NINDS and NIAID recruited other ICs to the NIH research program including the National institute for Environmental Health Sciences (NIEHS), the National Eye Institute (NEI), the National Institute for Child Health and Human Development (NICHD), the national Institute of General Medical Sciences (NIGMS), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Library of Medicine (NLM), and the National Heart, Lung and Blood Institute (NHLBI). Several other ICs participated in NIAID-sponsored biodefense related meetings where the overall strategy was discussed.

In FY 2006, NINDS, with the encouragement and support of NIAID, established the NIH "Countermeasures Against Chemical Threats" (*CounterACT* (**http://www.ninds.nih.gov/counteract**) research program to support basic, translational, and clinical research into chemical threat agents. The CounterACT network continues to be a critical piece of the NIH strategic plan and is aimed at the discovery and/or identification of better therapeutic and diagnostic medical countermeasures against chemical threat agents.

The scope of research includes:

- Mechanistic studies to identify targets for therapeutic development
- Development of in vitro and animal models for efficacy screening
- Efficacy screening of therapeutics using new and validated in vitro and animal models
- Advanced efficacy studies with appropriate animal models using Good Laboratory Practices (GLP)
- Clinical trials

Beginning in Fiscal Year (FY) 2005, the NIH received supplemental funds to address the effect of radiation and nuclear threats on human health. In FY 2006, an additional supplement of $50 million was appropriated to address medical countermeasures against chemical terrorist threats to civilian communities. These supplemental funds were sustained until FY 2010. In FY 2011, the funding was reduced to $49.5M. At present, the FY 2012 funding and beyond has not been determined at the writing of this document.

The need to utilize the expertise and investments of the Department of Defense is considered a key element in the overall biomedical research effort for the nation, since military research and development priorities overlap with those of civilians, including the needs of civilian first responders and health care providers.

Interagency Agreements (IAAs) were initiated in 2006 with the U.S. Army Medical Research and Materiel Command (USAMRMC) and its subsidiary laboratory, the U.S. Army Medical Research Institute of Chemical Defense (USAMRICD). Subsequently, in 2011, NIH established IAAs with the U.S. Army Defense Technical Information Center (DTIC) and the U.S. Army Edgewood Chemical Biological Center. These IAAs expedite the production and use of restricted chemical warfare agents under DoD control. The IAA research agenda compliments the CounterACT grant program.

The Chemical Countermeasures Research Community

Since its creation, CounterACT has sought to engage high quality scientists in a variety of disciplines to include neuroscience. For example, CounterACT supported a Nobel Laureate to develop novel therapies to treat nerve agent poisoning. To recruit scientists, NIH uses a variety of funding announcements (Appendix 3). In 2006, the NIH received over 100 applications for this research which were then evaluated by an external review panel of experts, in keeping with long-standing NIH practice and stated NIH peer review policy. Of these applications, more than 60 new investigators received funding in September 2006. Continuing to move the program forward, many new initiatives were released subsequently, including–

- 2008 – two additional initiatives that funded seven additional projects and two Research Centers of Excellence.
- 2009 – initiatives to foster partnerships with industry through the NIH Small Business Innovation Research/Small Business Technology Transfer (SBIR/STTR) program.
- 2010 and 2011 – new and renewal proposals solicited by NINDS for research resulting from projects funded in 2006. (Appendix 3)

The CounterACT Program

The Trans-NIH CounterACT Program encompasses a network of milestone-driven cooperative projects, including six Research Centers of Excellence, 54 individual research projects, small business awards and six Interagency Agreements with the DoD. CounterACT sponsors annual meetings of the entire research network (see *NIH Record* article for a description- **http://nihrecord.od.nih.gov/newsletters/2009/06_26_2009/story5.htm**) to foster collaboration, share information and resources, and to give federal officials a chance to see progress. Several CounterACT scientific specialty groups also hold workshops and meetings between annual meetings.

The CounterACT program staff is in close contact with the Center for Scientific Review which receives, screens, and reviews more than 60,000 investigator-initiated research proposals per year. Some grants from this pool that are relevant to the CounterACT mission have been funded through the CounterACT research network.

The NIH Biodefense Research Coordinating Committee conducts regular reviews of the research investments for the program to ensure that resources are directed towards developing only the most promising countermeasures. Interim reviews of the CounterACT Program are conducted by an external panel of senior academic experts and government officials to ensure that CounterACT activities are in keeping with NIH standards of research excellence.

A number of resources and facilities provide additional access and collaboration opportunities to CounterACT researchers:

- The NIH-supported CounterACT Efficacy Research Facility at Battelle Laboratories in Ohio increases the capacity for conducting studies with restricted agents and those needed to fulfill FDA Animal Rule requirements. The facility has a long-standing partnership with the DoD.
- The CounterACT Preclinical Development Facility developed with SRI International enables investigators to conduct preclinical studies needed for drug discovery and development and, ultimately, FDA approval. Studies approved by the NIH are performed at no cost to the researcher.
- The NINDS Anticonvulsant Screening Program at the University of Utah has been supported for the past 30 years to screen for anticonvulsant compounds for treating seizures caused by epilepsy and other pathologies. CounterACT leverages the high level of expertise and experience at this facility in a separate tract to screen for new drugs to treat seizures caused by chemical threat agents.

This program works closely with the MRICD program to test promising compounds with real chemical warfare agents that cannot be tested or used elsewhere.

- Researchers funded through the NIH can use the NIAID-supported Collaborative Research Facility at USAMRICD in Edgewood, Maryland. This controlled research laboratory, suitable for research on concentrated chemical agents, was built in partnership with the DoD. The facility allows collaboration between highly experienced biochemists, physiologists, veterinarians, and laboratory technicians at USAMRICD and investigators from academic institutions.

Research Accomplishments Resulting from NIH Support of Chemical Threat Research

The NIH primary research effort on exposure to chemicals, particularly agents identified as threats by DHS, has focused on their potential effects on public health. Despite the potential use of chemicals as terrorist weapons, NIH research into chemical agents has been labeled "unclassified." This has allowed research, including studies conducted jointly by NINDS and DoD-supported scientists, to be published, presented at professional scientific conferences, and in cases of intellectual property, to be awarded patents (Fig. 3). The following section describes selected findings resulting from NIH support for research into chemical threat agents.

Progress Against Nerve Agents

Chemicals that have toxic effects on the nervous system represent one of the largest challenges in medical therapeutics. NIH has been in the forefront of research to develop safe and effective countermeasures to combat the effects of chemical nerve agents for the civilian population and has capitalized on existing research infrastructures to accomplish new goals

CounterACT studies of nerve agents include the following examples:

- Diazepam, a controlled anti-anxiety drug, which is used to treat seizures resulting from nerve agents and epilepsy. However, users can become habituated to diazepam. In partnership with the military, CounterACT-supported researchers are working to develop an anticonvulsant against nerve agents for use in place of diazepam. Midazolam has been approved by the FDA as an anesthetic. It is water soluble, more quickly absorbed, and effective more rapidly than diazepam. Now, researchers are developing midazolam in an intramuscular (IM) form and are evaluating its use in treating seizures caused by nerve agents like sarin or soman. Phase I studies for midazolam IM in humans are complete and final animal studies are being led by the DoD. Midazolam IM is expected to be approved and ready for procurement by the HHS and DoD in 2013/2014.
- The CounterACT Program supported a clinical trial to compare a midazolam IM auto-injector, which could allow for the delivery of midazolam to patients before they arrive at the hospital, with Lorazepam IV, another treatment for seizures in humans. This trial used the same drug and auto-injector device proposed for use in humans exposed to nerve agents. The goal was to determine whether the new drug (midazolam IM) was at least as good as the standard of care (lorazepam IV). The results of this study were published in the New England Journal of Medicine (2102) in a landmark study indicating that not only does midazolam IM work as well as Lorazepam IV, but in fact works better and faster in humans. This study will be essential for the 2012 New Drug Application to the FDA. Additional research into anticonvulsant drugs, through the IAAs with USAMRICD, is being performed to determine if the drugs can be administered as adjuncts (an additional drug) to nerve agent antidotes. This adjunct method would help

enhance anticonvulsant efficacy (midazolam) when treatment is delayed following exposure. These results will complement the current CounterACT midazolam efforts and address HHS and DoD concerns.

- Galantamine is an FDA-approved drug used to treat Alzheimer's disease. Galantamine can "protect" the brain from nerve agents by a reversible, competitive acetylcholinesterase (AChE) inhibition mechanism, according to CounterACT-supported researchers. However, the specific actions of galantamine that contribute to its effectiveness as a therapeutic countermeasure against organophosphate (OP) poisoning still remain poorly understood are presently being studied. CounterACT is supporting advanced efficacy studies in small animals and non-human primates in preparation for human safety trials.
- At the Uniformed Services University of the Health Sciences, researchers supported by CounterACT have discovered a new class of anticonvulsant and neuroprotectant drugs that prevents seizures and the damage caused by nerve agents. One drug identified reduced the damage caused by nerve agents even after the onset of seizures. The safety of the drugs in this class are being tested concurrently at the CounterACT preclinical contract facility. Preliminary results revealed that drugs in this class enhance anticonvulsant efficacy, minimize brain injury, and facilitate behavioral recovery.
- Oximes are molecules that counteract the effects of nerve agents by reactivating an enzyme that nerve agents turn off. The FDA approved one such oxime as an antidote to most CW nerve agents, but it is less effective against other neurotoxins. Novel oxime compounds are needed that can cross the blood-brain barrier and that are effective against a broader range of nerve agents. Such antidotes have been developed in CounterACT laboratories and through the IAAs. The possible addition of a centrally active oxime to the current regimen of atropine sulfate and 2-PAM could prove to be beneficial in the treatment of nerve agent intoxication. Nobel Laureate researchers, in the CounterACT Program, have synthesized several compounds that are now being tested against a variety of nerve agents and will be further tested for their safety in preclinical studies.

Progress Against Metabolic Poisons

Chemicals, like hydrogen cyanide and the cyanide salts, can function as metabolic poisons that interfere with cellular respiration and starve the cell of oxygen. Symptoms can range from dizziness to unconsciousness, shallow breathing, low blood pressure, and death within minutes. Cyanide can be a major threat to public health when deliberately added to food and drink or released as a gas. Treatments for cyanide exposure must be quick and safe to administer without waiting for laboratory confirmation. Currently, there are FDA-approved drugs that help counteract the effects of cyanide. However, the treatment is complex, can be dangerous, and most antidotes need to be given IV. Health practitioners and the military need new drugs that are fast-acting, safe and easily administered in mass casualty situations.

Advances for treating exposure to cyanide include the following:

- Cobinamide is a chemical precursor in cobalamin (vitamin B12) biosynthesis. Cobinamide can bind cyanide with greater affinity than hydroxycobalamin, which is a different cyanide antidote that was recently approved by the FDA. In animal studies conducted through the CounterACT Program, cyanide research centers in Minnesota and California have shown that cobinamide has great potential as an antidote for lethal and non-lethal doses of cyanide poisoning in animals. Importantly, this compound can be rapidly administered intramuscularly with an auto-injector device. These initial results have

moved cobinamide to pre-clinical development and eventual licensure. This drug holds promise as a countermeasure against cyanide attacks and accidental exposures.

- Compounds such as sulfanegen show promise as an antidote to cyanide exposure because they render the metabolic poison (cyanide) nontoxic in animal studies. This molecule has a different mechanism of action than cobinamide. Investigators at the CounterACT cyanide research center are investigating the possible use of cobinamide and sulfanegen together, and comparing the effectiveness of these combinations to existing cyanide countermeasures.
- Researchers at the University of Pittsburgh identified a new mechanism of cyanide poisoning involving nitric oxide. The understanding of this mechanism could lead to more effective treatments.
- A diagnostic assay developed through the CounterACT Program can detect cyanide exposure in humans. This assay capitalizes on the high affinity and binding capacity of cyanide to cobinamide. Its detection limit is similar to that of the existing standard clinical assay used at present. More importantly, one can obtain measurements immediately, rather than the current 24 hour time lag. The high affinity cobinamide assay was used in a successful clinical trial of a drug that generates cyanide in patients. Investigators in a parallel study are developing this assay as a hand-held device to be used in the field for real-time cyanide measurement. The prototype will be applicable to blood, urine, and saliva samples.

Progress Against Vesicants and Pulmonary Agents

Vesicants and pulmonary agents are common chemicals that cause injury to the skin and lungs following exposure. These agents include sulfur mustard and chlorine. Upon long-term exposure, the lungs will develop thick, fibrin clots which cause severe damage to the tissues.

Advances against vesicants and pulmonary agents include the following:

- CounterACT researchers from the National Jewish Medical and Research Center in Denver, CO, identified an antioxidant, AEOL 10150, that can protect animals against exposure to vesicants and pulmonary agents. In combination with other therapy, AEOL 10150 was shown to block the processes that damage lungs and other tissues. Other groups at the Center determined that the drug PEGylated Thrombopoietin-mimetic peptide (TPOmp) could serve as a therapy for chemically induced bone marrow suppression. The potential benefits of AEOL 10150 and TPOmp against chemical agent toxicity is complemented by the Radiological Nuclear Medical Countermeasures Program to develop them as a treatment for acute radiation exposure. This could lead to new drugs for use against both types of threats.
- Doxycycline is a tetracycline antibiotic that has been shown to be protective in several models of sulfur mustard poisoning. Some promising studies indicate that it may be useful in treating vesicant-induced eye injuries. Preliminary data from a CounterACT-funded study also suggest that the cyclooxygenase (COX) inhibitor, indomethacin, may be effective in mitigating skin damage and lung injuries caused by sulfur mustard. Corticosteroids such as clobetasol propionate reduce the severity of superficial skin injuries induced by liquid sulfur mustard and bromine vapor. Indomethacin, in conjunction with the drug diclofenac, works well when given in the days following exposure. IAA studies show that valproic acid, vigabatrin, and ambrisentan therapies may significantly increase survival rates when administered 15-20 minutes after exposure.
- CounterACT researchers at the University of Alabama at Birmingham, showed that the FDA-approved, B2-agonist, Brovana™, reverses chlorine-induced reactive airway

syndrome in mice. Combined therapy with Brovana TM and antioxidant drugs such as N-acetylcysteine and ascorbate, appears highly effective in counteracting the pulmonary toxicity of chlorine.

- IAA researchers have shown that anti-inflammatory treatment, soon after injury, may limit tissue damage and speed wound healing for both superficial and deep dermal injuries. IAA researchers at the USAMRICD has been working on drugs, such as etanercept, for systemic treatment of deep dermal injury with some promising results. When applied topically in combination with clobetasol propionate and diclofenac (non-steroidal anti-inflammatory drug), inflammation and fibroplasia have been reduced.

Therapeutic Targets and Model Development

Therapeutic targets and model development are primary goals for the NIH medical chemical defense program. Rapid medium and high throughput screening models are needed to screen various drugs and chemicals in order to develop antidotes for various countermeasures against threat agents. Targeted therapies are being funded by the NIH to develop strategies and identify mechanisms required for the development of medical countermeasures against terrorist chemical threats.

NIH-supported Research Advances toward therapeutic targets and model development include the following:

- CounterACT-supported investigators in Miami have identified a novel target and therapeutic approach for nerve agent poisoning. The approach stabilizes the expression of an enzyme–acetylcholinesterase which is critical to the interaction between nerves and muscles, and prevents its removal by natural processes. The resulting pool of active enzymes can be available when other enzymes are destroyed by nerve agents and pesticides. Follow-up studies targeted this stabilization process using a laboratory-generated protein that binds enzymes at the neuromuscular junction. These NIH-funded studies represent the first approach (in decades) to treat organophosphate and nerve agent poisoning.
- Transient Receptor Protein Antigent-1 (TRPA1) is a stress sensor involved in signal transduction and initial host responses to chemicals. This response includes the release of cytokines and other immunologic mediators. These mediators may lead to unintended damage to surrounding tissues. CounterACT-funded researchers have sought to identify strategies to diminish the collateral tissue damage induced by TRPA1 and related proteins. In these studies, TRPA1 deficient mice were exposed to a TRPA1-antagonist, HC-030031. These mice had a reduced response to toxic chemical challenges. The results strongly suggest that TRPA1 contributes to the development of acute inflammation. Other studies are underway to determine how cell injury occurs and how the signal transduction pathways leading to cell damage might be interrupted. CounterACT researchers at Yale have discovered that in signal transduction, the TRPA1 receptor is activated by diphosgene, chloropicrin, isocyanates and other chemicals.
- NIH-supported researchers are investigating water soluble derivatized fullerene nanoparticles to reduce the effect of nerve agents. These researchers are performing experiments to learn if the nanoparticles are able to scavenge nerve agents. For example, at the University of Puerto Rico, studies have indicated that cembranoid compounds, isolated from the tobacco plant, offer protection to the nervous system from nerve agents. Additional compounds are being studied as possible neuroprotectants. Novel compounds being examined include the growth factor neuregulin, prostaglandin receptor ligands and glutamate receptor antagonists.

- Development of rapid medium- and high-throughput screening models for chemical medical countermeasures is a goal for the NIH program. One NIH funded study at Harvard has developed a new high-throughput screen for nerve agents and pesticides using zebra fish and two physiological responses that have been validated against higher order mammalian models. The same system is being used by another Harvard researcher in a separate project to screen for antidotes for cyanide. These studies have demonstrated that at different developmental stages, organisms vary in their sensitivity to cyanide. This may have implications as to susceptibility of children and may guide medical interventions.
- A screening program supported by CounterACT is located at the NIH Molecular Libraries Screening Center at Scripps Institute in California. The purpose of this program is to find compounds that can serve as antidotes to the chemical threat agent anatoxin. This involves two prominent marine neurotoxin experts at the Scripps Ocenaographic institute and the best resources available at the Scripps Screening Center.

Looking To The Future

When the medical chemical defense NIH research program started five years ago, the national research infrastructure in the United States for medical chemical research community was largely limited to those institutions directly funded by DoD. That effort focused almost solely on the warfighter. With the development of a strategic plan and research agenda and the maturation of the NIH research effort against chemical threats, substantial progress has been made in developing scientific interest and expertise in the private and public research sectors. Partnerships between the Federal Government, academia and industry are well underway. A robust research effort involving universities and drug developers is now engaged in medical chemical defense research that addresses the needs of the civilian community. The program has attracted allies of the U.S. who have similar needs for safe and effective medical products for military and civilian use. Promising drugs in development under this program have potential applicability in both malicious and accidental events.

Hazardous chemical threats continue to be a great concern. Knowledge of the toxicity of chemicals raise concern among those who have national security responsibilities and those health care providers who must care for the casualties, but unfortunately this knowledge has attracted the attention of extremists with thoughts on how such chemicals could accomplish their more sinister goals. More recently, attention has focused on widely available household chemicals that could be used in malicious ways and those toxic chemicals that have been used in suicide.

From the onset of the program, the need for medical interventions that address all subsets of the civilian population was recognized. Special concerns for pregnant women, infants and children (where growth and development may be more affected by chemical exposure) means the development of appropriate animal models that simulate the human experience is of high concern to the public. A long-term goal addressed in the initial Strategic Plan alludes to understanding effects of chronic exposure and developing protective or preventive drugs administered concomitantly with initial therapy. To achieve this, animal models will need to be developed that mimic the human experience. Research tools are needed to study the chronic effects of exposure.

The NIH CounterACT program has engaged the varied strengths of the agency. This emphasis will continue at the NIH and also with other governmental departments and agencies to include the military, as well as all disciplines of science and medicine.

Toxic industrial chemicals (TICs) are of increasing importance due to their ready availability and high toxicity. Most highly toxic TICS fall outside the purview of the Chemical and Toxins Weapons Convention. These chemicals may have damaging effects on the body via direct contact with skin and mucous membranes or through inhalation as a gas, vapor, or aerosol. Some TICs, such as household chemicals or poisons, have been used in small quantities in suicide or assassination. It is important to note that TICs could be employed on a larger scale. Therefore, NIH interaction with poison control centers across the nation is another partnership that has evolved through this ongoing research effort.

Research into nerve agents remains a high priority for the NIH, especially because adversaries could potentially use new neurotoxic agents against civilian populations. It is now recognized that many toxic chemicals affect neurotransmission via different pathways. Because many toxic chemicals affect neurotransmission via different pathways, new treatment modalities likely will involve new combinations of drugs. The central nervous system has several important neurotransmitters other than acetylcholine, to include some that are excitatory (e.g., glutamate), and others that are inhibitory (e.g., GABA). Specific receptors determine the rate and severity of neurotoxicity. Organophosphate research is necessary to extend the understanding of how toxic chemicals affect different neurotransmission pathways, as well as other organ systems of the body.

The CounterACT research efforts will continue to focus on medical product development using the existing mechanisms supporting research. The goals and objectives of the 2007 *National Strategic Plan and Research Agenda for Medical Countermeasures against Chemical Threats* remain largely unchanged, with the exception of a growing emphasis on TICs. Emphases include efforts to:

- Integrate into standards of emergency care of products that meet the needs of the community.
- Continue assessing whether medical products already licensed for use in the United States are applicable to chemical casualty care.
- Assess products for civilian applications which are developed for military use; this is part of the overall HHS preparedness and response strategy.
- Develop or improve medical diagnostic tests and assays that detect the presence of specific chemicals or their metabolities in body fluids.

Much more needs to be accomplished through the NIH medical chemical countermeasures research programs. Since its inception, the research effort have invested heavily in addressing well-established chemical threats of concern, but many other toxic chemicals have yet to be studied in terms of their mode of injury and opportunities for therapeutic intervention. Much is still unknown of long-term consequences of exposure of most chemicals. With a viable research community now established through the NIH program, a strong partnership has been established between the NIH and academia, industry and the government. The NIH efforts will continue to be directed at discovery and development of safe and effective interventions that address the greatest terrorist threats.

Appendix 1. Examples of Highly Hazardous Chemicals

Chemicals Affecting the Nervous System (toxicity on the central and/or peripheral nervous system)

- Tabun (GA)
- Sarin (GB) and related derivatives
- Soman (GD) and related derivatives
- Cyclosarin (GF)
- VX and related chemicals
- R-33 (R-VX)
- TETS (2,6-dithia-1,3,7,7 tetraazadamantane 2,2,6,6 tetraoxide)
- Anatoxin (algal toxin)
- Mercury compounds (e.g., methyl and dimethyl mercury)
- Aldicarb (pesticide)
- Brodifacoum (pesticide)
- Chlorpyriphos (pesticide)
- Parathion
- Fentanyl and related compounds (opiates)

Chemicals Affecting the Skin, Eyes and Mucous Membranes (often referred to as irritants)

- Sulfur Mustard (HD) (vesicant)
- Nitrogen Mustard (vesicant)
- Lewisite (L) (vesicant)
- Phosgene Oxime (CX)
- Hydrogen Selenide
- Hydrogen Chloride
- Fuming Sulfuric Acid
- Hydrogen Fluoride (anhydrous form)
- Sodium Azide
- Arsenic Compounds (trivalent forms, e.g., Arsenic Trioxidc)
- Chloropicrin
- Ammonia
- Mercury (vapor form)

Chemicals Affecting the Lower Respiratory Tract (capable of causing lung injury, i.e., pulmonary edema)

- Chlorine
- Phosgene
- Diphosgene
- Perfluoroisobutylene (PFIB)
- Phosphine (rodenticide)

Note: Many irritant chemicals deeply inhaled in high concentrations may cause pulmonary edema

Chemicals Affecting Cellular Respiration (poisons damaging cellular metabolic enzyme systems)

- Hydrogen Cyanide (AC)
- Potassium Cyanide
- Cyanogen Chloride (CK) (irritant also)
- Hydrogen Sulfide
- Thalium Sulfate (especially chronic exposure)
- Acrylonitrile (metabolized to cyanide)

Appendix 2. Key Workshops and Expert Panels on Chemical Threats and Medical Countermeasures*

Title	Location	Year	Goals
NIAID Expert Panel Workshop on Chemical Threats and Medical Countermeasures	Washington, D.C.	2004	Identify research gaps and priorities for chemical threat agents (first NIH meeting to determine the scope of future NIH research investments).
NINDS Counterterrorism and Neuroscience Workshop	Washington, D.C.	2004	Identify research gaps and priorities for chemical threat agents that target the nervous system.
NIH Anticonvulsant Expert Panel	Bethesda, Maryland	2005	Identify potential anticonvulsant agents that could be used to treat seizures caused by nerve agents; set research priorities.
NIH Cyanide Expert Panel	Bethesda, Maryland	2005	Identify gaps and priorities for research on cyanide toxicity and medical interventions.
NIH Pulmonary Agents Expert Panel	Bethesda, Maryland	2005	Identify research gaps and priorities for chemical threat agents that target the airways.
NIH Blue Ribbon Panel on Chemical Threats and Medical Countermeasures	Bethesda, Maryland	2006	Develop consensus set of recommendations related to research gaps and research priorities for chemical medical countermeasures.
NINDS Research Centers of Excellence Technical Assistance Workshop	Rockville, Maryland	2006	Provide information and answer questions regarding preparation of proposals in response to the NIH Research Centers of Excellence request.
NIH Expert Panel on Toxic Vesicants	Rockville, Maryland	2007	Identify gaps and priorities for research on sulfur mustard toxicity and medical interventions.
NIH Expert Panel Workshop on Toxic Industrial Chemicals - Pesticides and Pulmonary Edemagenic Chemicals	Bethesda, Maryland	2009	Identify gaps and priorities for research on toxic industrial chemicals and pesticides, and on chemicals that cause pulmonary edema.
NIH Expert Panel Workshop on Cyanide	San Francisco, California	2010	Review the current status of research and development regarding medical interventions for CN exposure; identify needs for future research, diagnostics, and methods of treatment suitable for different populations.

*This list does not include regularly scheduled meetings to review CounterACT Program grants, progress reports with IAAs (U.S. Army), interagency meetings, threat assessment determinations, or meetings with BARDA/ASPR/HHS.

Appendix 3. NIH CounterACT Announcements Soliciting Research Proposals

2006 .....

RFA-NS-06-004 Countermeasures Against Chemical Threats (CounterACT) Research Projects (U01)

RFA-NS-06-005 Countermeasures Against Chemical Threats (CounterACT) Research Centers of Excellence (U54)

RFA-NS-06-006 Countermeasures against Chemical Threats (CounterACT) Small Business Innovation Research (SBIR/U44) Awards for Therapeutics Development (U44)

RFA-NS-06-007 Diagnostic Technologies for Chemical Threat Exposure Small Business Innovation Research (SBIR/U44) Awards

RFP–NS-04-01 Identification and Characterization of Novel Therapeutics for the Treatment and Prevention of Epilepsy (for nerve agent anticonvulsant – see below)

RFP-NS-06-04 Countermeasures Against Chemical Threats (CounterACT) Preclinical Development Facility

2008 .....

RFA-NS-08-003 Countermeasures Against Chemical Threats (CounterACT) Advanced Development Cooperative Agreements (U01)

RFA-NS-08-004 Limited Competition for Countermeasures Against Chemical Threats (CounterACT) Research Centers of Excellence (U54)

2009 .....

PA-09-080 PHS 2009-02 Omnibus Solicitation of the NIH, CDC, FDA and ACF for Small Business Innovation Research Grant Applications (Parent SBIR [R43/R44])

PA-09-081 PHS 2010-02 Omnibus Solicitation of the NIH for Small Business Technology Transfer Grant Applications (Parent STTR [R41/R42])

2010 .....

NOT-NS-10-011	Notice of Intent to Publish Funding Opportunity Announcements for Countermeasures Against Chemical Threats (CounterACT) Cooperative Research Projects (U01) and Research Centers of Excellence (U54)
PAR-10-019	Countermeasures Against Chemical Threats (CounterACT) Exploratory/Developmental Projects in Translational Research (R21)
PAR-10-180	Countermeasures Against Chemical Threats (CounterACT) Cooperative Research Projects (U01)
PAR-10-181	Countermeasures Against Chemical Threats (CounterACT) Research Centers of Excellence (U54)
PA-10-050	PHS 2010-02 Omnibus Solicitation of the NIH, CDC, FDA and ACF for Small Business Innovation Research Grant Applications (Parent SBIR [R43/R44])
PA-10-051	PHS 2010-02 Omnibus Solicitation of the NIH for Small Business Technology Transfer Grant Applications (Parent STTR [R41/R42])

2011 .....

PAR-11-155	Countermeasures Against Chemical Threats (CounterACT) Cooperative Research Projects (U01)
PA-11-096	PHS 2011-02 Omnibus Solicitation of the NIH, CDC, FDA and ACF for Small Business Innovation Research Grant Applications (Parent SBIR [R43/R44])
PA-11-097	PHS 2011-02 Omnibus Solicitation of the NIH for Small Business Technology Transfer Grant Applications (Parent STTR [R41/R42])

Appendix 4: 2006-2010 CounterACT Centers of Excellence and Primary Investigators

Lovelace Biomedical & Environmental Research Institute

Albuquerque, New Mexico

Mohan Sapori, Ph.D.

"Identification of Therapeutics for the Treatment of Sulfur Mustard Injury"

University of Medicine and Dentistry of New Jersey - Rutgers University

Piscataway, New Jersey

UMDNJ - Robert Wood Johnson Medical School

Jeffrey D. Laskin, Ph.D.

"Sulfur Mustard Research and Medical Countermeasures"

U.S. Army Medical Research Institute of Chemical Defense

Edgewood, Maryland

David E. Lenz, Ph.D.

"Catalytic Bioscavengers Against Nerve Agents"

University of Alabama at Birmingham

Birmingham, Alabama

Sadis Matalon, Ph.D.

"Novel Treatments of Chlorine Induced Injury to the Cardio-Respiratory Systems"

University of Minnesota Center for Drug Design

Minneapolis, Minnesota

Steven Patterson, Ph.D.

"Combined Use of Cobinamide and a 3-Mercaptopyruvate Prodrug for Cyanide Poisoning"

National Jewish Medical and Research Center

Denver, Colorado

Carl W. White, M.D.

"Novel Antioxidant Therapeutics for Sulfur Mustard Toxicity"

Appendix 5: Interagency Agreements (IAAs)

5.1. Anticonvulsant research: funded through the "Chemicals Affecting the Nervous System – Anticonvulsants / Neuroprotectants" program:

- 2011-2012: Y1-OD-1563-01: Received by USAMRICD
- 2010-2011: Y1-OD-0692-01: Received by USAMRICD
- 2009-2010: Y1-OD-9613-01: Received by USAMRICD
- 2008-2009: Y1-AI-6178-03: Received by USAMRICD
- 007-2008: Y1-AI-6178-02: Received by USAMRICD
- 2006-2007: Y1-AI-6178-01: Received by USAMRICD

5.2. Cyanide research: funded through the "Cyanide Diagnostics and Efficacy Testing of Next Generation Cyanide Antidotes" program:

- 2011-2012: Y1-OD-1561-01: Received by USAMRICD
- 2010-2011: Y1-OD-0690-01: Received by USAMRICD
- 2009-2010:
  - Y1-OD-9611-01: Received by USAMRICD
  - Y1-OD-9611-02: Received by USAMRICD
- 2008-2009: Y1-AI-6176-03: Received by USAMRICD
- 2007-2008: Y1-AI-6176-02: Received by USAMRICD
- 2006-2007: Y1-AI-6176-01: Received by USAMRICD

5.3. Pulmonary research: funded through the "Chemicals Affecting the Respiratory Tract – Pulmonary Toxicant Gases" program:

- 2011-2012: Y1-OD-1564-01: Received by USAMRICD
- 2010-2011: Y1-OD-0693-01: Received by USAMRICD
- 2009-2010: Y1-OD-9614-01: Received by USAMRICD
- 2008-2009: Y1-AI-6179-03: Received by USAMRICD
- 2007-2008: Y1-AI-6179-02: Received by USAMRICD
- 2006-2007: Y1-AI-6179-01: Received by USAMRICD

5.4. Vesicant research: funded through the "Chemicals Affecting the Skin, Eyes, and Mucous Membranes – Toxic Vesicants and Industrial Chemicals" program:

- 2011-2012: 1-OD-1562-01: Received by USAMRICD
- 2010-2011: 1-OD-0691-01: Received by USAMRICD
- 2009-2010: 1-OD-9612-01: Received by USAMRICD
- 2008-2009: Y1_AI-6177-03: Received by USAMRICD
- 2007-2008: Y1-AI-6177-02: Received by USAMRICD
- 2006-2007: Y1-AI-6177-01: Received by USAMRICD

5.5. Chemical Countermeasures: Studies to Support Countermeasures for Highly Toxic Materials Including Chemical Agents and Toxins

- 2010-2011: Y1-OD-0387-01: Received by DTIC

IAA Recipients:

DTIC: Defense Technical Information Center

USAMRICD: U.S. Army Medical Research Institute of Chemical Defense

5.6 Chemical Countermeasures Collaboration

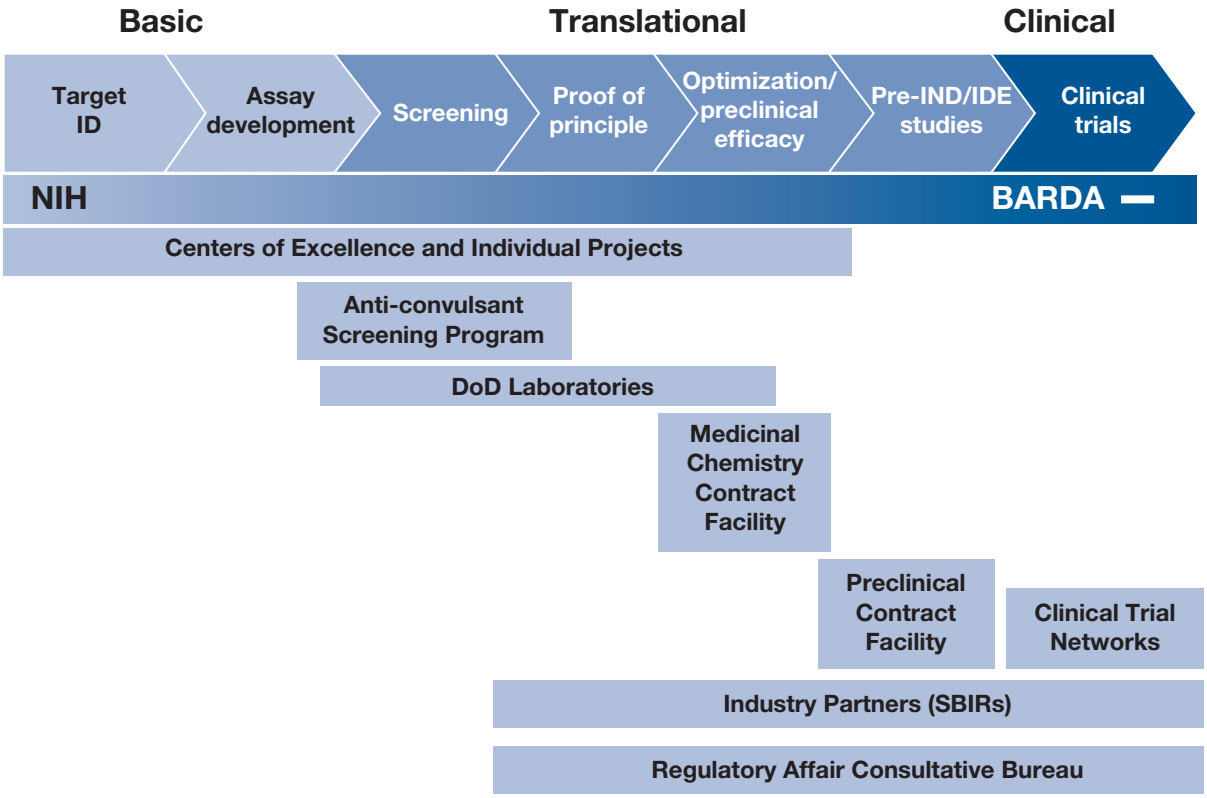
- 2011-2012: DOD/NIH InterAgency Agreement: Received by DoD

IAA Recipients:

DoD: Office of the Assistant to the Secretary of Defense for Chemical and Biological Defense and Chemical Demilitarization (DATSD(CBD/CD)), Washington, DC

ECBC: U.S. Army Edgewood Chemical Biological Center, Aberdeen Proving Ground, MD

Figure 4.1. Overview diagram of CounterACT Program



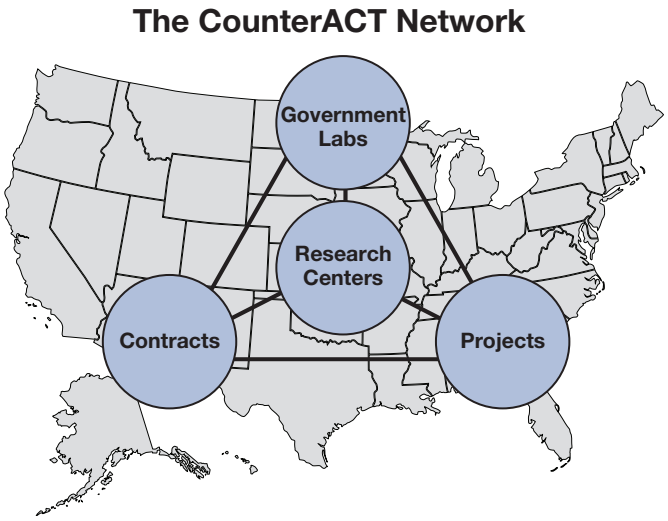
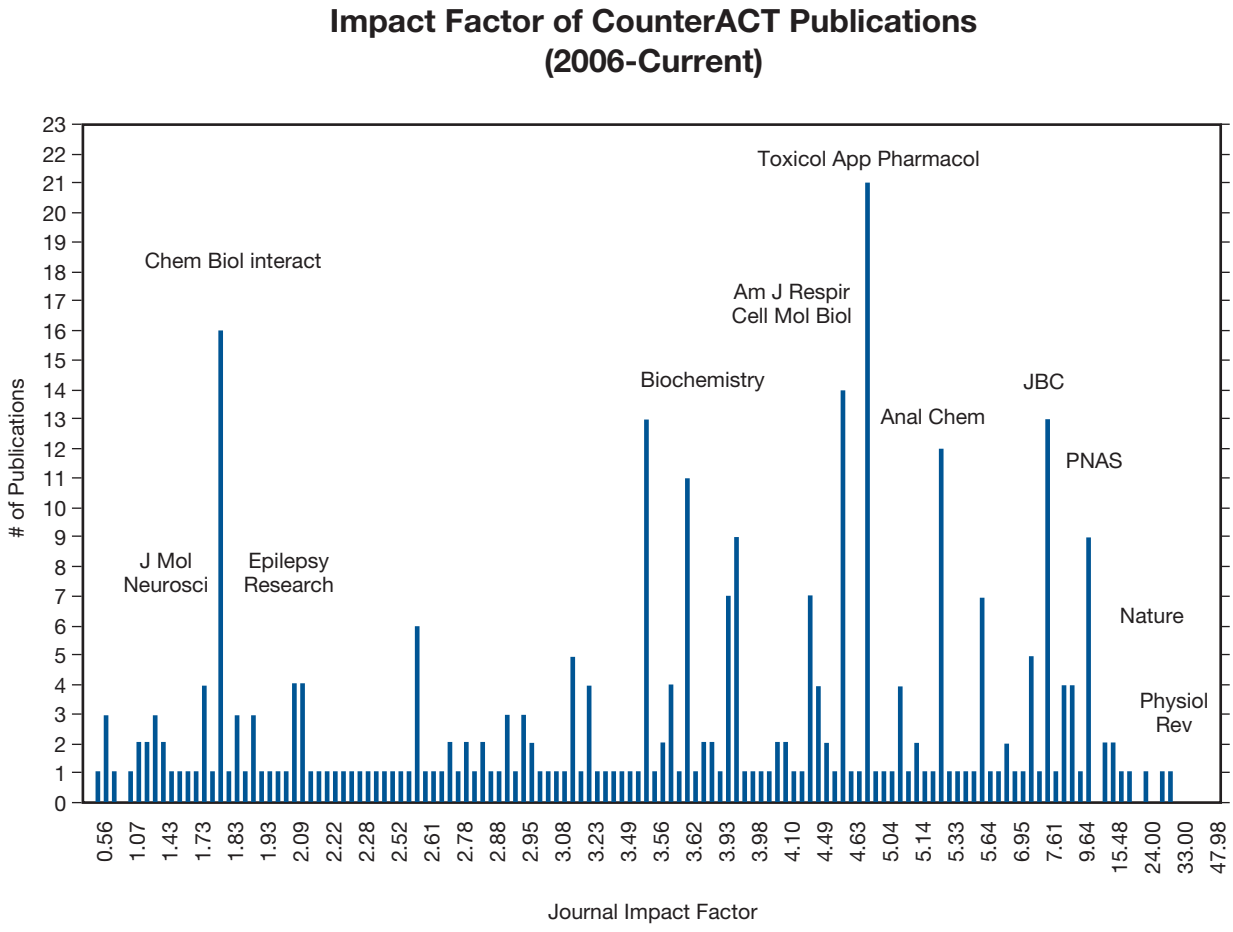


Figure 4.2. Examples of NIH CounterACT Medical Candidate Countermeasures and Department of Health and Human Services Technical Readiness Levels (TRLs)

Activities	TRL		Specific Candidate Countermeasures
Target identification	1	Basic (NIH)	Over 30+ "hits" and/or targets identified
Validated screening tool	2		
"Hit" identification	3		
Preliminary leads (proof of concept)	4	Applied (NIH)	Neuregulin; AEOL 10150 Brovana*; Sulfanogen
Optimized leads (pre-clinical)	5		
Candidate drug	6		Cobinamide; Galantamine*
IND ready	7	Advanced (NIH & BARDA)	
Phase 1	8		
Phase 2	9		
Phase 3 (definite animal efficacy)	10		
Licensure, approval, clearance	11	Acquisition (HHS)	Midazolam*
Post-licensure and post-approval activities	12		
Expanded efficacy (if appropriate)	13		

*Denotes FDA-approved compound

Figure 4.3. Publications Resulting from CounterACT Investments. (345 total as of May 2011)



The impact factor of CounterACT publications from 2006 to the present has been noteworthy. The impact factor represents a measure reflecting the average number of citations to articles published in science and social science journals and is frequently used as a proxy for the relative importance of a journal within its field. The quality and volume of publications in peer-reviewed journals is indicative of the high quality of research (and researchers) which are involved in the NIH medical chemical defense program. The figure displays the # of publications and the quality of journal. The publication record is a critical product of the program and should be used as a criteria for success for the CounterACT program.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

NIH…Turning Discovery into Health

National Institute of Allergy
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