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**Pharmaceutical Defenses for  
Warfighters and First Responders:**

# **THE NEBRASKA DRUG DISCOVERY AND DEVELOPMENT PIPELINE (ND<sup>3</sup>P)**

A CONCEPT PAPER FOR U.S. DEPARTMENT OF DEFENSE STAKEHOLDERS



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# EXECUTIVE SUMMARY

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The “business” of defense is complex and multifaceted. One of the most urgent needs of those who put their lives on the line every day for the protection of the people of the United States is mitigation of the physical, human damage that happens in the field of battle. There is a constant search for ways to protect the warfighter with methods ranging from time-tested mission strategies and innovative tactics to new types of armor and weapons and the use of diplomacy to prevent conflict in the first place.

In the modern world, the most insidious threats in battle involve technological weapons — biological, chemical and radiological. Fortunately, even as these threatening technologies become increasingly sophisticated, researchers are using the same advances in knowledge and science to prevent and treat the damage caused.

In many cases, pharmaceutical drugs can be used to protect soldiers (and civilians) both before and after exposure to biological, chemical and radiological weapons. However, these types of pharmaceuticals do not always offer a promise of profitability, so the traditional pathways to development are often closed.

The Nebraska Drug Discovery and Development Pipeline (ND<sup>3</sup>P) was created to fill this gap. Drawing on existing resources, personnel and processes that have evolved through past connections with the National Strategic Research Institute (NSRI), its sponsor (U.S. Strategic Command: STRATCOM) and numerous Department of Defense customers, the pipeline is led and contributed to by University of Nebraska researchers and is poised to take orders for American forces’ next-gen pharmaceutical defenses.



# UNDERSTANDING THE THREATS

The intentional or unintentional release of biological agents, chemical agents and radioactive weapons during war is not something that happens every day. But the United States federal government knows, as a nation, we need to be ready for any day that one of these events does happen. In fact, because of the potential devastation they can cause, mitigation of these threats has become a national priority of the United States Department of Defense (DOD).

The impact of the Covid-19 pandemic throughout most of 2020 and into 2021 emphasizes our world's substantial vulnerability and the need for protection from destructive compounds, regardless of their source. The United States, as well as our neighbors in every other country of the world, will most certainly face similar future challenges associated with zoonotic diseases and pathogenic threats we have yet to encounter. Few would argue that we must do everything we can to be ready for the next one.

There is a long history of humans using biological, chemical and radiological weapons to inflict damage upon enemies, but recent advances have brought this concern into the mainstream with a new intensity. In addition to intentional destruction caused during war, the same toxic compounds are still threats when their impact upon the human population is unintentional.



## BIOLOGICAL THREATS

Unintentional biological threats and their associated damage are sometimes the most challenging to manage because the spread is gradual and less noticeable than acute events. This is true in the case of diseases in Third World countries, for example, where the destruction of diseases such as tuberculosis, malaria, yellow fever, Ebola and other

potential pandemics tend to easily gain a foothold because resources and knowledge are scarce. For developed countries, out of sight is often out of mind, and a disease can cause great destruction before we know our neighbors need help.

To make matters worse, when a disease breaks out in a far-off country, it doesn't stay isolated within that geographic area as diseases often did before the early 19th century. Modern air travel now makes it possible to visit nearly any location in the world. Businessmen and businesswomen, as well as families, military personnel, leisure travelers and aid workers are constantly traversing the globe — and bringing viruses and other diseases with them. In this way, the population of the world is more vulnerable than it ever has been to biological threats.



## CHEMICAL THREATS

Unintentional chemical damage to humans comes with events such as industrial spills or agricultural run-off and release of additives from tires to the atmosphere. When intentional, negligent or natural events lead to contamination of the environment, entire population centers can find themselves at risk of injury.



## RADIOLOGICAL THREATS

Accidental radiological damage has the potential to spread in similar ways when nuclear power plant cores are breached, experiments go wrong or manufacturing mistakes are made. For example, both the 2011 accident at the Fukushima Daiichi nuclear energy facility in Japan and the Chernobyl accident in the former Soviet Union in 1986 required countermeasures to protect the public.





All of these threats to the happiness and health of humanity are well known and often discussed in many circles, from scientific labs and diplomatic institutions to parent groups, courts of law, media offices and environmental activist organizations. Biological, chemical and radioactive compounds cause some of the world's most insidious ailments.

As the collective intellect of humanity advances, and as we increasingly manipulate naturally occurring compounds, whether for nefarious or admirable goals, it is likely that we will see these ailments at an increasing rate in the decades to come.

**In many cases, all that is needed to stop a pandemic, mitigate physical damage or reduce lives lost is a targeted, tested pharmaceutical drug. Some prevent damage from happening in the first place. Others treat those who have been exposed in an attempt to reduce ongoing effects. However, obstacles stand in the path of producing such drugs, from a lack of funding to regulatory hurdles and the need for the right animal model(s).**

One serious obstacle is more likely than others to keep protective drugs from being manufactured: there is often little financial incentive to develop and manufacture them, and drug development, especially in the later stages, is nearly impossible without the backing of a pharmaceutical company.

"Big, safe, human trials take time and money," said Dr. Rebecca Oberley-Deegan, associate professor of biochemistry and molecular biology at the University of Nebraska Medical Center and ND<sup>3</sup>P contributor. "It is just impossible to do as a startup. You have to have government or a pharma company in place. Grants are not enough to support a phase three trial."

This financial incentive obstacle represents a loss not only of possible funding from highly profitable pharmaceutical companies but also a loss of opportunities to tap into the knowledge and experience of the world's most advanced drug development experts.

# COLLABORATING TOWARD SOLUTIONS

The Nebraska Drug Discovery and Development Pipeline (ND<sup>3</sup>P), with the help of the National Strategic Research Institute (NSRI) at the University of Nebraska, is designed specifically to respond swiftly to the need for prevention mitigation of biological, chemical and radiological threats — both intentional and unintentional. The ND<sup>3</sup>P is a multidisciplinary, cross-campus initiative that draws on expertise, facilities and technology that already exists in the state of Nebraska and at the University of Nebraska.

NSRI, a highly varied and multidisciplinary institute, is one of only a handful of DOD-designated University Affiliated Research Centers (UARCs) in the United States. The institute's association with its sponsor, U.S. Strategic Command in nearby Bellevue, Neb., and other DOD customers, gives it a unique ability to connect diplomats, researchers, clinicians and others across normally unbreachable lines to solve some of the world's most pressing problems in support of the

warfighter. Although NSRI is specifically focused on supporting soldiers and first responders, many of the projects translate to civilian medical, law enforcement and governing needs.

In partnership with NSRI, the ND<sup>3</sup>P's infrastructure and its coordinated, collaborative network give it the ability to respond to biological, chemical and radiological threats quickly and with experience-based clarity and confidence. The rapid response capabilities of the ND<sup>3</sup>P for developing drugs to fight these diseases provides an important and badly needed global defense.

The resulting drug discovery and development infrastructure not only streamlines the research and development of clinical therapeutic agents in general but is also well positioned to respond to the DOD's pursuit of "orphan drugs" that are not profitable to produce but are essential to keeping warfighters and first responders safe.



**"Having an overall goal expressed clearly and consistently is important. A lot of times that gets lost in our individual research projects. ND<sup>3</sup>P provides us with the platform that helps take our research from the bench to the bedside and even to the battlefield."**

**DR. REBECCA OBERLEY-DEEGAN**

**ASSOCIATE PROFESSOR OF BIOCHEMISTRY AND MOLECULAR BIOLOGY  
UNIVERSITY OF NEBRASKA MEDICAL CENTER**



**“Acute Radiation Syndrome is definitely not a disease I thought about before getting involved. The need is obvious and makes complete sense. I wouldn’t have thought of our research being able to contribute to this.”**

**DR. TOMAS HELIKAR**

**SUSAN J. ROSOWSKI ASSOCIATE PROFESSOR OF BIOCHEMISTRY  
UNIVERSITY OF NEBRASKA-LINCOLN**

Through ND<sup>3</sup>P, many of the researchers are using their skills and resources in unexpected ways that benefit defense. For example, radiation exposure causes acute radiation syndrome (ARS), which is an ailment resulting from the massive inflammatory response induced by exposure to ionizing radiation. It can kill a person within days unless mitigative steps are taken. The ND<sup>3</sup>P has partnered with the Federal Government to develop desperately needed drugs that could be used to protect our citizens and soldiers in the event of a radiological event.

For all of the team members, being involved in the defense of the nation is an added personal benefit.

The founding principle of the ND<sup>3</sup>P is that discovering and developing promising lead compounds to FDA approval can be achieved by leveraging the coordinated expertise and resources of its networks. In effect, the pipeline is a highly collaborative “virtual pharmaceutical company” that represents a truly transformative and meaningful change in the way drugs are developed.



**“There is a patriotic aspect of helping the country and protecting our troops using the tools of biomedical science. That’s something that has made this project special for all of us.”**

**DR. DAVID BERKOWITZ**

**ND<sup>3</sup>P CO-DIRECTOR  
WILLA CATHER PROFESSOR OF CHEMISTRY, DEPARTMENT CHAIR  
UNIVERSITY OF NEBRASKA-LINCOLN**



# TRAVELING THROUGH THE NEBRASKA DRUG DISCOVERY AND DEVELOPMENT PIPELINE

Drug development is an incredibly complex undertaking that involves the coordination of multiple scientific endeavors. This is exactly the central function and strength of the ND<sup>3</sup>P. It serves as a drug agnostic, collaborative platform designed to develop molecules into useful pharmaceutical products. Although this concept was developed to advance “orphan drugs” or those drugs that are not of interest to Big Pharma, the ND<sup>3</sup>P can be used to advance any drug to FDA approval.

The drug development process occurs in three fundamental stages: early-stage drug discovery, advancing hit compounds to pre-clinical candidates, pre-clinical studies and clinical studies. Each of these stages require distinctive core capabilities, and they can be thought of as separately activable modules.

## 1. EARLY-STAGE DRUG DISCOVERY

The early stages of drug development — whether for civilian or military use — involves many activities, including the basic science needed to identify and validate drug targets, development of assays that provide a reliable and reproducible way to determine drug activity, high-throughput screening capabilities that allow for rapid screening of inhibitory activity of hundreds of thousands of molecules, and informed drug modifications with the goal of improving the activity of a given candidate therapeutic agent or combination of agents.

These experimental screening capabilities are amplified under the rich network of experience and resources of the ND<sup>3</sup>P and complemented by building a robust in silico screening platform with

targeted hires and software/hardware acquisitions and maintenance. This allows hundreds of millions of molecules to be screened virtually. Continued investments in structural biology at both UNL and UNMC are planned to support this in silico screening platform with the needed high-resolution structural data upon which it is based and tested.

The NU system offers expertise in all of these areas that could be coordinated to focus on specific targets as part of ND<sup>3</sup>P activities. Each of these functions is capable of standing alone and supporting basic biomedical research but could also be activated for targeted studies when needed to support the mission of the ND<sup>3</sup>P and the needs of the DOD.

The ND<sup>3</sup>P will strengthen its expertise in medicinal chemistry, which is needed to modify molecules in a way that improves their efficacy, decreases toxicity or enhances stability within an animal. The addition of faculty members who have expertise in medicinal chemistry will greatly increase the speed with which molecules can be modified to improve their drug-like properties.

In addition, this expertise will be complemented by a toxicology core designed to identify toxic effects that molecules might have on various tissues. Although toxicology studies typically are performed through contract research organizations (CROs), the ND<sup>3</sup>P will develop its own capabilities in this area to streamline these studies and provide a more cost-effective means to carry them out.

Other core capabilities important in drug development include drug formulation and delivery, assets that





are essential for the latter stages of development. All of these core capabilities are readily available to faculty within the NU system, as well as to external customers such as the DOD and other national defense customers.

Once the early stages of drug discovery are completed, initial hit compounds must be screened at the level of their ability to bind to the desired macromolecular target or elicit the desired phenotypic response. It is at this stage that the tools of medicinal chemistry and organic synthesis are brought to bear on the project to build focused libraries around the hit structures. Compound libraries are evaluated to optimize structure/function relationships; e.g., improving potency while maintaining the desired mode of interaction, specificity of binding, and selectivity.

Promising compounds are evaluated further using in vitro (cell culture-type) model systems and screened experimentally for off-target effects. This process produces lead compounds from the most promising hits, the best of which emerge as pre-clinical candidates.

Both UNL and UNMC have a strong tradition in medicinal chemistry and organic chemistry, and additional targeted hires are projected in these areas to support ND<sup>3</sup>P, the biomedical research missions of both campuses, and ultimately the targeted needs of warfighters and first responders.

## 2. PRE-CLINICAL STUDIES

Once pre-clinical candidates have been identified, in vivo studies on the performance of these molecules in animal models can begin. These studies include tests of toxicity, the way the molecules are metabolized within an animal in pharmacokinetics and pharmacodynamics studies, the efficacy of these compounds in appropriate disease models, and studies to optimize the formulation of these drugs. All of these studies require specialized skills and expertise and can be performed in various laboratories across the NU system.

## 3. CLINICAL STUDIES

Finally, once all of these studies have demonstrated that these drugs perform satisfactorily in animal models, they are ready for testing in humans. Phase 1 clinical trials are performed to assess the safety of the drug candidate; i.e., ensuring that side effects and any potential for toxicity of the drug candidate in humans is acceptable.

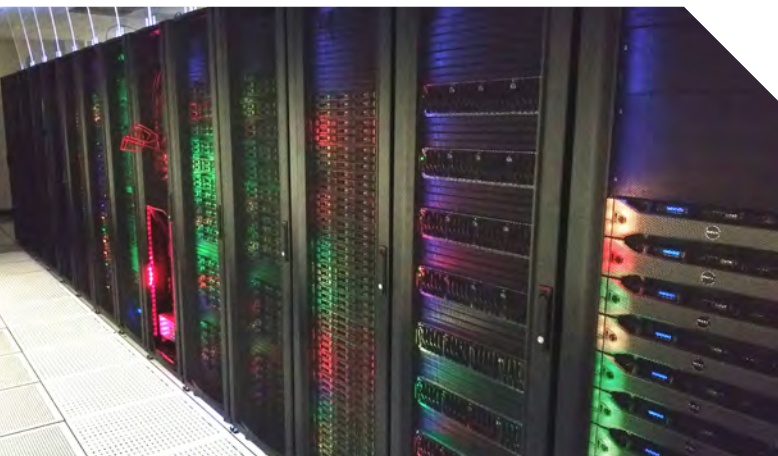
Next, Phase 2 clinical trials are performed using a limited number of patients to gain an initial assessment of efficacy in humans.

Finally, Phase 3 clinical trials are performed on a much larger cohort of patients to conclusively demonstrate the utility of a drug in the treatment of disease. All of these studies can be coordinated within the Clinical Research Center (CRC) at UNMC.

# NU FACILITIES, EQUIPMENT AND TECHNOLOGY—READY FOR THE MISSION

Past partnerships between the University of Nebraska and DOD customers have resulted in a cadre of research laboratories, technologies and personnel within the university system that are especially well-equipped to address DOD needs. This includes the nurturing of talent through one-of-a-kind educational experiences offered to interns and doctoral students, many of whom now work in defense-related disciplines and industries.

Below is a list of some of the centers within the University system that explicitly collaborate with ND<sup>3</sup>P and its defense clients.



## HOLLAND COMPUTING CENTER

University of Nebraska

Contains the fastest, most robust computing power in the state of Nebraska. NU researchers rely on the center for data storage and high-performance computing resources. The center also provides training resources and ongoing support.

## CENTER FOR DRUG DISCOVERY & LOZIER CENTER FOR PHARMACY

College of Pharmacy

University of Nebraska Medical Center

With 85,000-square-feet, this center provides state-of-the-art research and education space with next-generation technology to prepare future pharmacists and drug discovery scientists for the changing health care landscape using UNMC's innovative educational model. Research in areas of infectious diseases, neuroscience, cancer and rare disorders to expand drug discovery, specifically in medicinal chemistry and pharmacokinetics, take place within this secured lab space.



## CENTER FOR DRUG DELIVERY AND NANOMEDICINE

College of Pharmacy

University of Nebraska Medical Center

Serves to unify existing diverse technical and scientific expertise in biomedical and material science research at the University of Nebraska thereby creating a world class interdisciplinary drug delivery and nanomedicine program. This is realized by integrating established expertise in drug delivery, gene therapy, neuroscience, pathology, immunology, pharmacology, vaccine therapy, cancer biology, polymer science and nanotechnology at UNMC, UNL and Creighton University.

## NEBRASKA CLUSTER FOR COMPUTATIONAL CHEMISTRY

Department of Chemistry

University of Nebraska–Lincoln

Brings together expertise to continue to push experimentalists to find structures that have not already been seen or may be lying under the earth.

## BIOINFORMATICS AND SYSTEMS BIOLOGY CORE

College of Medicine

University of Nebraska Medical Center

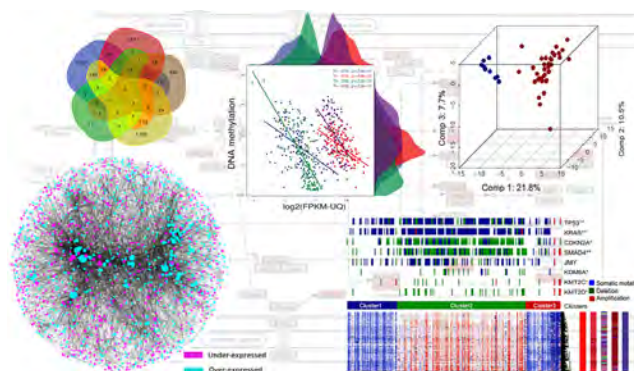
Leading the biological data analytics for ND<sup>3</sup>P, the bioinformatics and systems biology core at UNMC provides next-generation sequencing data analyses, data integration, interpretation and correlation of various types of system biology data, implements machine learning on 'bigdata' using high performance computers, and development of web applications and databases to enable users search and visualize results generated from the ARS project. The graphic shows various types of research data analyses carried out by the Bioinformatics and Systems Biology Core facility at UNMC.



## COMPUTATIONAL CHEMISTRY CORE

University of Nebraska Medical Center

Administers a site license of the Schrodinger software suite, one of the premier drug discovery software toolkits. There are currently more than 1.5 billion compounds that the core has curated for drug screening workflows. It has also implemented VirtualFlow, which uses several flavors of the popular AutoDock software to screen extremely large compound libraries against multiple drug targets. Core services include molecular modeling, drug screening, hit to lead optimization and molecular dynamics simulations.





Below is a list of some of the leading equipment and technology the university system has at its fingertips to use for ND<sup>3</sup>P work.

## HIGH-END 15 TESLA FOURIER TRANSFORM ION CYCLOTRON RESONANCE (15 T FT-ICR MS)

Department of Chemistry, University of Nebraska–Lincoln

Found only at a handful of academic institutions in the world, the quadrupole / Fourier transform ion cyclotron resonance mass spectrometer is equipped with a 15 T superconducting magnet, multiple ionization methods (conventional ESI; pump-driven and static-mode nanoflow ESI; MALDI), and multiple tandem mass spectrometry methods (beam-type and trapping-type CID; ETD and nETD; ECD and EDD; IRMPD). It is also fitted with an Advion TriVersa NanoMate for automated, zero-carryover sample introduction. This instrument is particularly well-suited for untargeted metabolomic analysis, intact protein characterization, and imaging of target compound distributions in tissues and other materials.



## NUCLEAR MAGNETIC RESONANCE

University of Nebraska–Lincoln

UNL has four Nuclear Magnetic Resonance (NMR) Spectrometers. NMR is used for a range of tasks, from checking synthetic compound purity to working out kinetic mechanisms of biological interactions. Three of these spectrometers have sample changers allowing for remote data acquisition. A range of NMR active nuclei can be observed on these NMR Spectrometers. The Bruker Avance III-HD 700 MHz NMR is the highest NMR magnet field in the state of Nebraska. Two of these NMR spectrometers are fitted with cryoprobes for increased sensitivity. One has solid-state NMR.



## BIOLOGICAL PROCESS DEVELOPMENT FACILITY

University of Nebraska–Lincoln

The BPDF offers biopharmaceutical process development and biomanufacturing services that transition discoveries into early-phase clinical trials. Capabilities include: master and working cell banks, upstream and downstream process development, stability testing services, analytical method development and qualification, and microbial manufacture of biologics. The BPDF has produced a wide range of biologics — including vaccines, recombinant proteins, gene therapies and other biotherapeutics — in partnership with government agencies, biotechnology companies, academic researchers and non-profit organizations. The BPDF applies decades of expertise and experience to developing scalable and reproducible cGMP manufacturing processes.





# INNOVATING TO PRODUCE PHARMACEUTICAL COUNTERMEASURES COST-EFFECTIVELY

Necessity is the mother of invention, and ND<sup>3</sup>P is the result of a pressing modern need: the development of pharmaceutical compounds that are not necessarily highly profitable but of great importance to our national defense.

The idea of the ND<sup>3</sup>P emerged directly out of NSRI, with leaders and researchers across the institute and NU campuses discussing the potential for such an initiative and concluding the need existed for the protection of soldiers and first responders and confirming that the solution could come from the University of Nebraska. In a way, this was a missing piece. The pipeline's partnership with NSRI and the DOD opens doors to funding, expertise and knowledge the team would not otherwise have access to.

In turn, NU, NSRI and the ND<sup>3</sup>P offer DOD customers access to a uniquely equipped toolbox filled with defense-related research, expertise and resources to address the protection of warfighters and first responders. In particular, the ND<sup>3</sup>P offers an easily accessed existing development system defense stakeholders can use as if it was their own to discover new pharmaceutical defenses.

This innovative, resourceful fusion of resources could very well provide pharmaceutical solutions unknown but needed to mitigate the next pandemic or mass casualty event. Ultimately, the ND<sup>3</sup>P could provide the nation's warfighters and commanders with the control, responsiveness and capability they will need to save lives in the face of new threats.

## REQUEST A MEETING

For more information about ND<sup>3</sup>P and the pipeline's capabilities and potential partnerships, visit [nsri.nebraska.edu/nd3p](https://nsri.nebraska.edu/nd3p) where you can also reach out to ND<sup>3</sup>P co-directors, Dr. Ken Bayles and Dr. David Berkowitz.



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