MEDICAL FUTURES STRATEGY

DOMANE

Discovery of Medical Countermeasures Against Novel Entities | DECEMBER 11, 2019

OVERVIEW

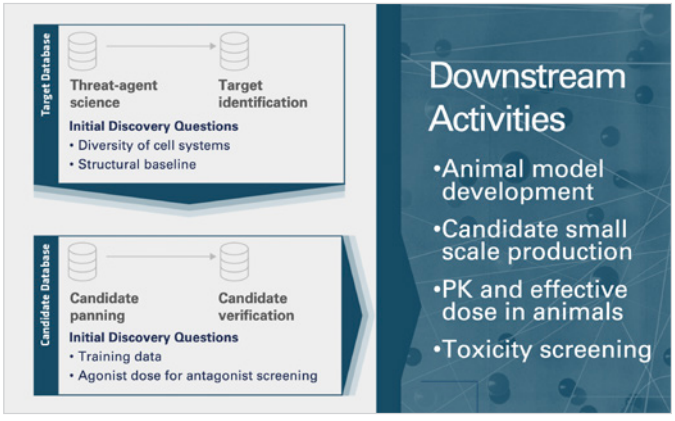
A core goal of the Joint Science and Technology Office (JSTO) for Chemical and Biological Defense (CBD) is enable the Warfighter to operate effectively within battlefields exposed to chemical and biological (CB) agents and avoid technological surprise. However, rapid growth in technological capabilities and vastly expanded knowledge base are fueling the broadening and accelerating threat agent development. As a result, it is crucial that the JSTO-CBD develop systems capable of rapid medical countermeasure (MCM) development to quash the risk of technological surprise.

Fortunately, there have been a multitude of technical developments that enable rapid *in vitro* toxicological assessment, precise structural resolution of novel MCM targets, and high-throughput MCM screening. Artificial intelligence (AI) systems and machine learning (ML) algorithms also hold promise to reduce the need for iterative laboratory-based target and MCM validation but currently lack the large data sets necessary to support predictive drug development. Although each of these technologies have potential to provide utility in and of themselves, there has yet to be an effort to fully integrate these platform technologies into a system of systems, which would enable the discovery of MCMs against novel entities and generate large data sets to support future AI/ML-driven rapid MCM discovery.

The intent of DOMANE is to bring together teams with diverse technical capabilities and identify an effective workflow that enables integration and rapid resolution of threat agent mechanism of action (MOA), MCM target discovery and MCM development. In doing so, DOMANE will create a broad candidate pipeline (*Figure 1*), which in turn will facilitate drug development against priority CB threats.

Figure 1 **Basic Science Strategy**

Figure 2 **Nominal DOMANE Workflow**



Detect the threats. Deter the actions. Defeat the enemy.

In order to de-risk, DOMANE proposes an independent but coordinated parallel development of platforms that address compartments of information, such as threat agent MOA, MCM target discovery and MCM verification. As these cornerstone components come online, the second stage of DOMANE will seek to integrate these parts into a system of systems capable of rapid end-to-end discovery of MCM against novel entities. Creating a fully integrated workflow (*Figure 2*), wherein each of the aforementioned compartments cooperate to generate lead MCM candidates will demonstrate the utility of DOMANE. In unravelling MOAs against CB threat agents, resolving structural targets and producing new MCMs will establish links between platform technologies and underwrite the transition of this approach to both advanced development and industry.

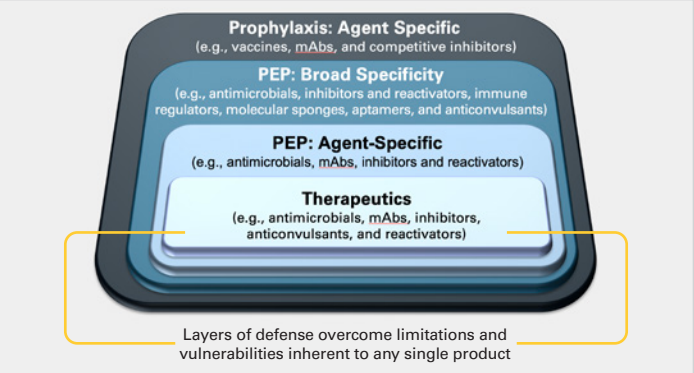
BACKGROUND

Keeping CB weapons in the Gray Zone[1] is aligned with the National Defense Strategy and the CBDP Enterprise Strategy. The rapid expansion of dual-use technologies such as 3-D printers and CRISPR-Cas, combined with the abundance of accessible knowledge and data, provide adversaries with the tools and know-how to develop an endless stream of CB threat agents. Although the art of the possible is limited by enduring CB constraints such as stability, delivery, and offensive utility, the potential for technological surprise is growing. Unique CB threats effective at sub-femtomole per kilogram doses that could avoid detection and impose immediate incapacitation may no longer be in the realm of science fiction. Moreover, the promise of such game-changing CB weapon technologies are likely too tempting for adversaries with different ethical values to resist. Accordingly, this future prospect cannot be ignored and delayed action to counter this looming danger could place the Warfighter at a technological disadvantage in the not too distant future. Moreover, maintaining a clear and present technological edge against CB weapons achieves a strategic U.S. advantage. The potential to counter rapidly any CB threat agent, therefore, operationally renders these weapons of mass destruction (WMD) as tools to prop up an insolvent regime or a last-resort, thereby greatly reducing the operational utility of CB Weapons.

DOMANE is not an isolated effort and works in concert with other JSTO-CBD developed strategies to reduce product risk, lifecycle cost and schedule for discovery of CB MCMs, as well as transition to advanced development. These strategies include LIMIT (Layered integrated medical intervention technologies) and LMOC (Limited MCM Operational Capability), which were developed to strengthen and broaden the CB MCM pipeline. LIMIT (*Figure 3*) is designed to bolster protection against target threat agents and avoid single-point of failure in the medical continuum of care. It also ensures MCM layers are interoperable, and creates MCM pipeline flexibility.

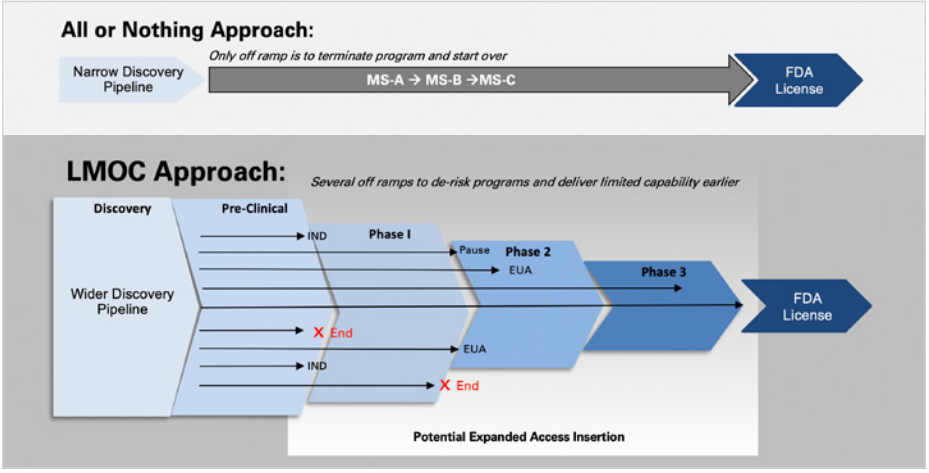
Figure 3 **Interoperable MCM Layers**

Widen protective barrier, additive or synergistic cooperation between layers, avoid interference between countermeasures



1. Operating in the Gray Zone. Countering Iran's Asymmetric Way of War, The Washington Institute for Near East Policy.

Figure 4 **Limited-Use MCM Operational Capability**



LMOC (*Figure 4*), on the other hand, is designed to enable the Warfighter the option to access to MCM early in the development cycle to identify mission- and theater-specific MCM needs. In doing so, LMOC will provide a mechanism to improve new MCMs prior to advancement to licensure and will stage products for rapid-launch of Phase 3 clinical trials. Together LIMIT and LMOC provide the strategies to optimize and manage MCMs as they mature along the drug-development pathway; in concert, the intent of DOMANE is to create an accelerated CB MCM discovery engine that creates a broad candidate drug pipeline to feed products through LIMIT into LMOC, and into advanced development based on Warfighter priorities (*Figure 5*). This approach contrasts with the CBDP legacy approach, which only needed to focus efforts on a limited set of CB targets.

In order to prepare for surprise in the form of novel, enhanced, or advanced threats, therefore, DOMANE will utilize and integrate platform technologies to create an efficient drug-candidate discovery workflow. In doing so, DOMANE will counter a broad variety of threat agents utilizing platform discovery, drug repurposing, drug design, drug manufacturing, and candidate-testing processes to harness the efficiencies offered by platform technologies and reduce developmental risks. DOMANE also will create potential to identify common targeting portals of CB threat, thereby providing knowledge baseline for MCM development against novel threats that target such portals. In addition, harnessing platform processes to target MCM development against novel CB threats enables DOMANE to tailor drugs rapidly without completely redeveloping key processes. Examples of platform processes in common use presently include cell-based test systems, cryo-electron-microscopy, learning data sets for AI/ML drug docking, manufacturing and testing, thereby minimizing schedule and cost requirements.

To initiate DOMANE, it is proposed that developers will assemble prototype systems comprised of platforms that will be assessed for their ability to identify threat MOAs, drug targets and drug candidates, using known threats to baseline the system, such as marine biotoxins and nerve agents. This builds up data sets for AI/ML, develops skills and efficiencies. These same technologies are then available for use in a crisis when a new threat is encountered. An example of a DOMANE workflow is showing in Figure 6. At this time potential components of DOMANE have been in development for several years and thus de-risked. For example, human organoid systems are currently being commercialized for toxicology studies and offer advantages over animal models. These organoid systems also have potential to enable mechanism of action studies and CB threat-agent target identification. Thus, standardized cell-based systems combined with cryo-EM (micro-ED) and AI/ML molecular docking technologies, has potential to integrate threat-agent science with the identification of lead MCM compounds. To connect this drug candidate discovery engine with downstream activities in the drug-development pathway, organoid systems based on animal species fit for laboratory experimentation will need to be developed to accelerate identification of animal models for MCM validation. DOMANE also will consider structural studies that characterize the vulnerabilities in critical systems

Figure 5 **Broad Drug Candidate Pipeline**

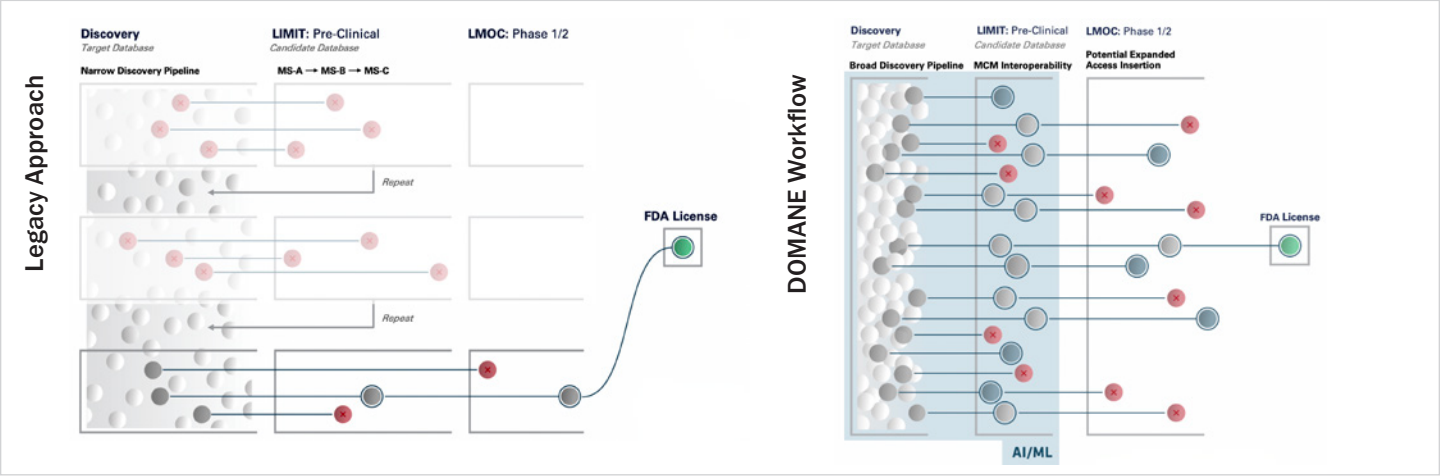
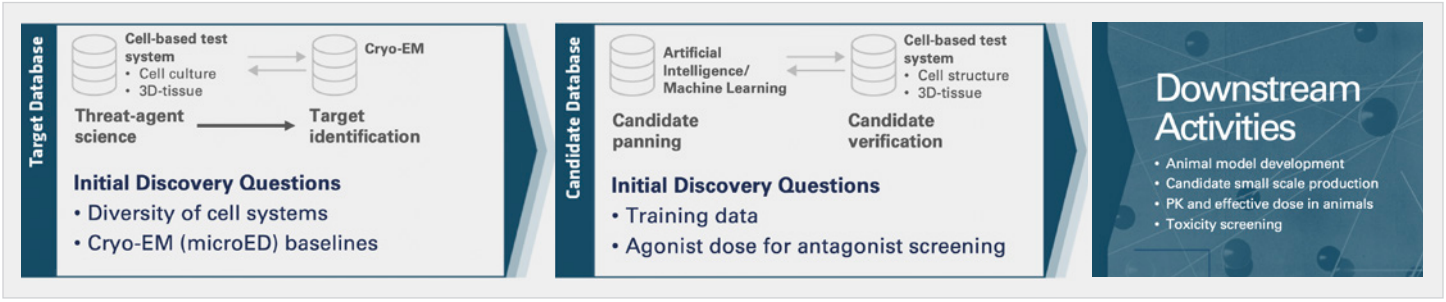


Figure 6 **Example DOMANE Workflow**



within bacteria, such as iron uptake, determine small-molecule solutions to supplant monoclonal antibodies, and offer avenues for novel drug targets. Also envisioned in DOMANE is to assess commonalities in biotoxin MOA, thereby identifying broad-spectrum solutions to this class of threats. In addition, development of strategies that enable screening of natural products from rain forest or marine sources to ensure generation of large training data sets. Such studies could incorporate proteomic, metabolomic, glycomic cryo-EM and AI/ML methodologies to identify novel compounds that competitively antagonize binding to all available human cellular targets, thereby preemptively identifying lead compounds that bind to and antagonize CB threat agent effects. Furthermore, DOMANE will also consider systems that enable high throughput target purification coupled with high throughput drug screening, to validate and refine initials lead compounds.

Successful development of DOMANE, therefore, will provide a candidate drug discovery and verification engine, which in months, not decades, will produce MCMs ready for pre-clinical and clinical development to render existing and novel CB threat moot, thereby maintaining Warfighter lethality in CB-threat contested spaces and avoiding technological surprise.