An Update from the Department of Defense for the Interagency Coordinating Committee on the Validation of Alternative Methods

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Objective

- Provide an annual update on the Department's activities related to alternative methods for toxicology testing for the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Public Forum

DoD Activities that Support ICCVAM

- Participating in ICCVAM Acute Toxicity Working Group; IVIVE Working Group; Ocular and Dermal Irritation Working Group; Read Across Working Group; Reproductive and Developmental Working Group; Skin Sensitization Working Group

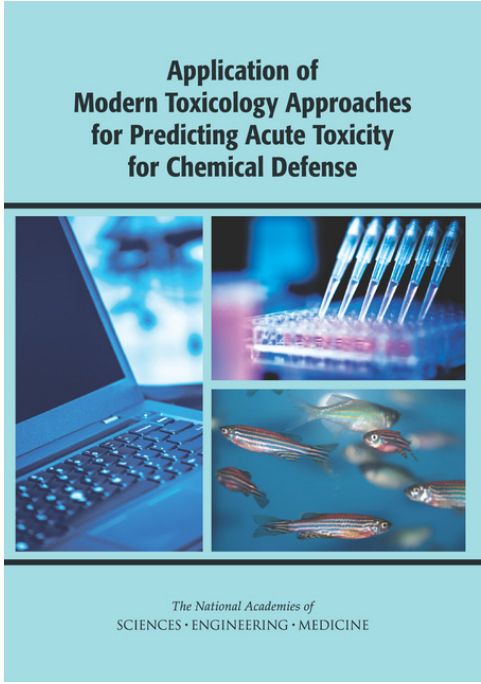
- Tri-Services Toxicology Consortium (TSTC)
  - Representatives from relevant DoD organizations
  - Share knowledge and ideas, collaborate on projects, and implement best practices

- One Health Initiative
  - Facilitates communication and collaboration across disciplines where the health of humans, animals, and the environment intersect

- Alternative animal models
  - Relative replacements of one species for another – i.e. - selecting species with lower neurophysiological development, when feasible

DoD Activities that Support ICCVAM

- "Application of Modern Toxicology Approaches for Predicting Acute Toxicity for Chemical Defense"
  - A report that resulted from a DoD-funded study performed by the National Academies of Sciences, Engineering, and Medicine, Committee on Toxicology
  - Task: Consider modern approaches for predicting toxicity and suggest an overall conceptual approach for using such information to help the DoD in its efforts to prevent debilitating, acute exposures to deployed personnel
  - http://dels.nas.edu/Report/Application-Modern-Toxicology- Approaches/21775



DOD Programs that Support ICCVAM

DARPA: Rapid Threat Assessment (RTA) Program

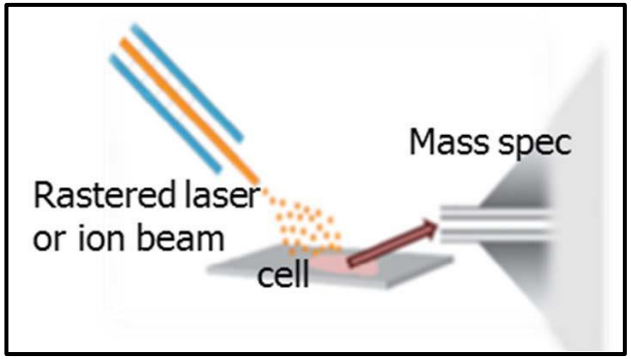
Problem: It takes many years to figure out how threats or drugs work

RTA Goal: In 30 days, figure out how a chemical, threat agent, drug, or biologic exerts its effects on biological systems

Potential Impact to ICCVAM: Significant decrease in time to understand mechanism of action, decrease in need for animal studies throughout process

Inspiration: New rapid mass spec imaging method

Mass Spectrometry Imaging



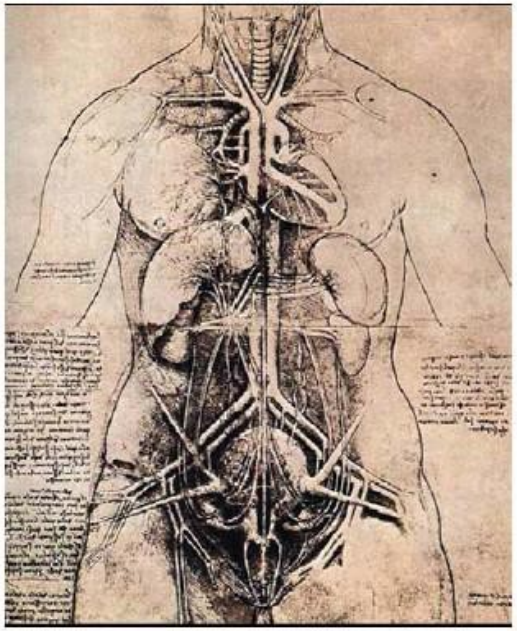
Status:

- 5 year program, approx. 20 months remaining
- 3 main performers – GWU, UC Boulder, Vanderbilt University
  - Proof of Concept Demonstration: Detected and identified the canonical mechanism of action of Bendamustine, a nitrogen mustard used as a chemotherapeutic, in 30 days.

DARPA Microphysiological Systems Program

Develop an *in vitro* platform that uses human tissues to evaluate the efficacy and toxicity of medical countermeasures.

In other words, build a human-on-a-chip:



- All ten human physiological systems will be functionally represented by human tissue constructs:
  - Circulatory
  - Endocrine
  - Gastrointestinal
  - Immune
  - Integumentary
  - Musculoskeletal
  - Nervous
  - Reproductive
  - Respiratory
  - Urinary
- Tissue viability for at least 4 weeks.
- Commercialization plan.

Status: 5 year program, in middle of 5th year

MIT-Completing platform development with 10 interacting organ systems (lung, gut, liver, pancreas, kidney, muscle, heart, brain, endometrium, skin)

Harvard/Wyss-Completing development of organ chips (lung alveolus, lung airway, heart, kidney proximal tubule, kidney glomerulus, gut, liver, blood brain barrier, bone marrow placenta)

DTRA: Ex vivo Countermeasure Evaluation and Licensure (XCEL) Program

XCEL: Development of Integrated-multi-organs-on-a-chip platforms to revolutionize assessment and evaluation of threat agents and medical countermeasures for chemical and biological defense and beyond

ATHENA – Los Alamos National Laboratory	ECHO – Wake Forest Institute of Regenerative Medicine
Liver and Cardiac Organoids (working on lung and kidney)	Liver and Cardiac Organoids
Modular microfluidics	Functional Assessment (Reactivity) and long-term viability
Universal Media Development	Bioprinting – augments function and controls spatial distribution
Ion Mobility – Mass Spectroscopy analysis of analytes/metabolites	Modular microfluidic system with rejuvenating in-line sensors

DTRA: Computational Rapid Identification Scientific Threat AnaLysis (CRISTAL)

Objective: Develop & integrate "non-testing approaches" that bring together multiple property evaluations & toxicity factors to enhance predictive characterization & toxicology for threat agents. Enable rapid understanding of the relative threat of chemical substances, particularly in terms of operational hazard posed to the warfighter.

Limited laboratory validation of physicochemical property prediction

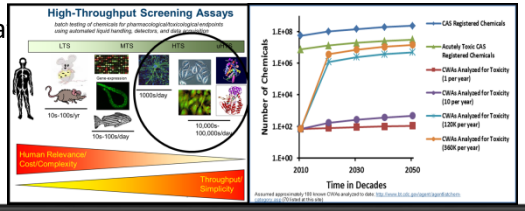
Molecular structure and Physicochemical properties
- Structure-activity relationship (SAR)
- Quantitative structure-activity relationship (QSAR)
- Quantitative Structure-property rela (QSPR)

ADME (*in vitro*) Assay validation of predictions

ADME Predictions based on QSAR modeling
- Mechanism of action prediction
- Identify potential nodes of convergence with known chemicals

***In vivo* toxicity validation**

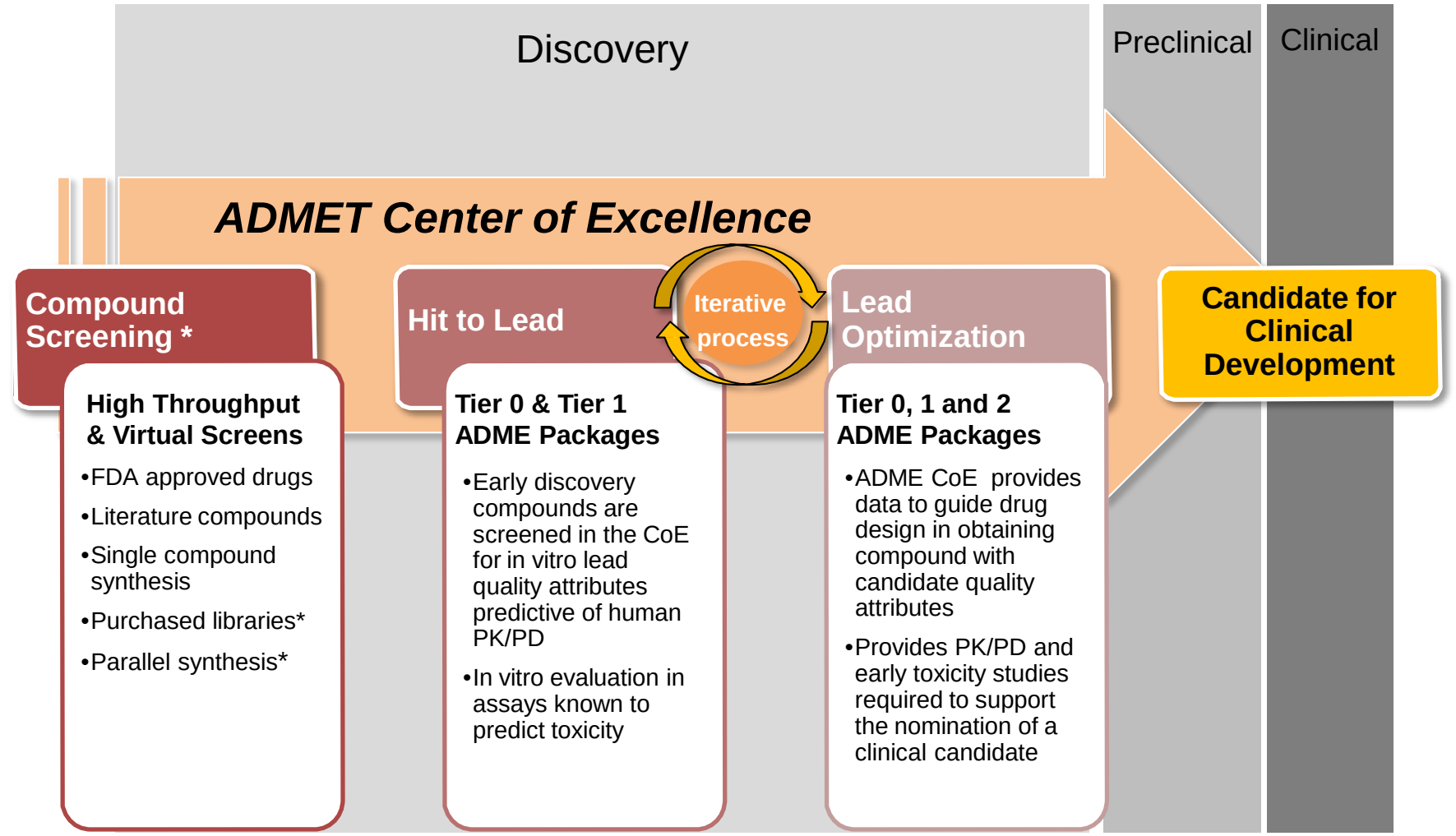
Acute toxicity predictions
- Dermal
- Inhalational
- Neurotoxicity
- Cytotoxicity



Analysis of 1000 Toxic Compounds
1000 years , $15B OR
1 year, $5M to $100M

JSTO shall develop integrated computational and in vitro predictive models to assist in identifying those current and emerging chemical biochemical materials that have the potential as CB threats of concern to the force. (FY15-19 PIP)

MRICD: Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) Center of Excellence



* Includes High Throughput Screening, Virtual Screens, rational drug design and/or pharmacology screens

Summary

- In partnership with other Federal agencies, academia, and industry, the Department of Defense remains committed to refine, replace, and reduce reliance on animal models when scientifically valid

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