Biosecurity and Biomedical Research: How Can We Succeed in Both?

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Legitimate Uses of Biological Materials

Botulinum Toxin

- It is the most acutely toxic substance known, with a median LD_{100} of 1 ng/kg (iv).
- Botulinum toxin occurs in nature and is produced by bacteria.
- Researchers discovered in the 1950s that injecting overactive muscles with minimal quantities of botulinum toxin type A:
  - decreased muscle activity by blocking the release of acetylcholine at the neuromuscular junction thereby rendering the muscle unable to contract for a period of 3 to 4 months
  - Alan Scott, an ophthalmologist first applied doses of the toxin to treat strabismus and blepharospasm
  - Partnership with Allergan to gain regulatory approval to market his discovery as a drug.
  - Allergan bought the rights to the drug in 1988 and received FDA approval in 1989 and renamed the drug Botox.

Botox

- Besides its cosmetic application, Botox is used in the treatment of:
  - Cervical dystonia (a neuromuscular disorder involving the head and neck)
  - Severe primary axillary hyperhidrosis (excessive sweating)
  - Achalasia (failure of the lower oesophageal sphincter to relax)
  - Migraine and other headache disorders
- Thus botulinum toxin is both an important therapeutic and research tool.
- It is also prominently listed on the select agents list

HHS SELECT AGENTS AND TOXINS

- Abrin
- Botulinum neurotoxins
- Botulinum neurotoxin producing species of *Clostridium*
- Cercopithecine herpesvirus 1 (Herpes B virus)
- *Clostridium perfringens* epsilon toxin
- *Coccidioides posadasii/Coccidioides immitis*
- Conotoxins
- *Coxiella burnetii*
- Crimean-Congo haemorrhagic fever virus
- Diacetoxyscirpenol
- Eastern Equine Encephalitis virus
- Ebola virus
- *Francisella tularensis*
- Lassa fever virus
- Marburg virus
- Monkeypox virus
- Reconstructed replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all eight gene segments (Reconstructed 1918 Influenza virus)
- Ricin
- *Rickettsia prowazekii*
- *Rickettsia rickettsii*
- Saxitoxin
- Shiga-like ribosome inactivating proteins
- Shigatoxin
- South American Haemorrhagic Fever viruses
  - Flexal
  - Guanarito
  - Junin
  - Machupo
  - Sabia
- Staphylococcal enterotoxins
- T-2 toxin
- Tetrodotoxin
- Tick-borne encephalitis complex (flavi) viruses
  - Central European Tick-borne encephalitis
  - Far Eastern Tick-borne encephalitis
  - Kyasanur Forest disease
  - Omsk Hemorrhagic Fever
  - Russian Spring and Summer encephalitis
- Variola major virus (Smallpox virus)
- Variola minor virus (Alastrim)
- *Yersinia pestis*

Research Uses of Biological Toxins

- Tetrodotoxins (TTX)
  - potent neurotoxin with no known antidote. Tetrodotoxin blocks action potentials in nerves by binding to the voltage-gated, fast sodium channels in nerve cell membranes.
  - Extremely useful in research areas of
    - Pain
    - Cardiac arrhythmias
    - Migraine
  - Select Agents Rule exempts 100mg quantities

Conotoxins

- The number of conotoxins whose activities have been determined currently is five:
  - α-conotoxin inhibits nicotinic acetylcholine receptors at nerves/muscles
  - δ-conotoxin inhibits the inactivation of voltage-dependent sodium channels.
  - κ-conotoxin inhibits potassium channels.
  - μ-conotoxin inhibits voltage-dependent sodium channels in muscles.
  - ω-conotoxin inhibits N-type voltage-dependent calcium channels.
- ω-conotoxin has an analgesic effect:
  - ω-conotoxin M VII A is 100 to 1000 times that of morphine.
  - A synthetic version of ω-conotoxin M VII A has found application as an analgesic drug ziconotide (Prialt).

Who Are Industry Scientists?

- We come from the same populations institutions as academic and government scientists.
- Focused on translational science and medical/clinical applicability.
- Short to medium term goals
- Operate in an environment where all tools are at their disposal – tremendous support infrastructure.
- Held to employment – dependent rules of conduct and accountability
- We also operate in a highly regulated environment with significant management oversight.

Industrial Laboratories and Personnel Characteristics

- Extensive training and documentation is required for all laboratory workers and scientists
  - Required training is both general and task dependent
  - Training and performance is proscriptive and tracked
  - Compliance with rules and regulations is a condition of employment
  - Regular laboratory and personnel inspections are required as part of the EHS Regulatory Management System.
  - 100% compliance is expected and required in order to maintain various outside accreditations and certifications (ISO14001, ALAAC, CDC, OSHA VPP)
- Thus the regulatory compliance mindset is an essential trait for technicians and scientists working in industrial laboratories.

A Balancing Act

- Biological toxins provide the essential tools by which biomedical researchers can study and develop new treatments for disease.
- Biological toxins also present a demonstrated laboratory and criminal hazard
- **How does one balance the risk – reward paradigm of using biological toxins in legitimate research?**

Some Thoughts from an Industry Perspective

- The Select Agents Program is a GOOD thing
  - Helped us to close the loop on accountability and added *teeth* to our internal biological safety management programs.
  - The quantity exclusion help us get rid of unused materials, reduce the risk of accidental release/loss, and reduced costs
  - Correctly based upon risk – benefit analysis
  - Science – based and data - driven

- Personal Reliability Programs will be tricky to implement and manage
  - Created for the nuclear weapons industry to control critical risk factors
  - The biomedical community is a much larger and heterogeneous group of individuals (i.e. military/contractor *versus* civilian scientists)
    - The initial gateway screening differs tremendously.
  - Who will decide the qualifying/disqualifying criteria for this population?
  - Will it need to be ADA compliant?
  - May need to be risk – adjusted according to relative and absolute risk associated with the agent (RG4).
  - Will be difficult to implement and apply a single set of risk criteria to this population.

Thoughts and Suggestions

- The infrastructure for regulation and control of industrial laboratory activities already exists and is in operation.
- The degree of regulation is risk – dependent and risk – adjusted.
- The Select Agents Rule was relatively to implement and comply with as significant controls and management systems were already in place:
  - Laboratory access
  - Inventory controls
  - Procurement controls
  - Laboratory Inspections
- *Personal reliability* is going to be difficult to implement
  - Legal rules regarding eligibility for employment
  - ADA
  - Work – place discrimination
  - Psychological screening?
  - Productivity impacts