TAB 3C

Dual Use Research of Concern

promoting understanding ▪ cultivating responsibility

An Educational Tool Developed Under the Auspices of the National Science Advisory Board for Biosecurity

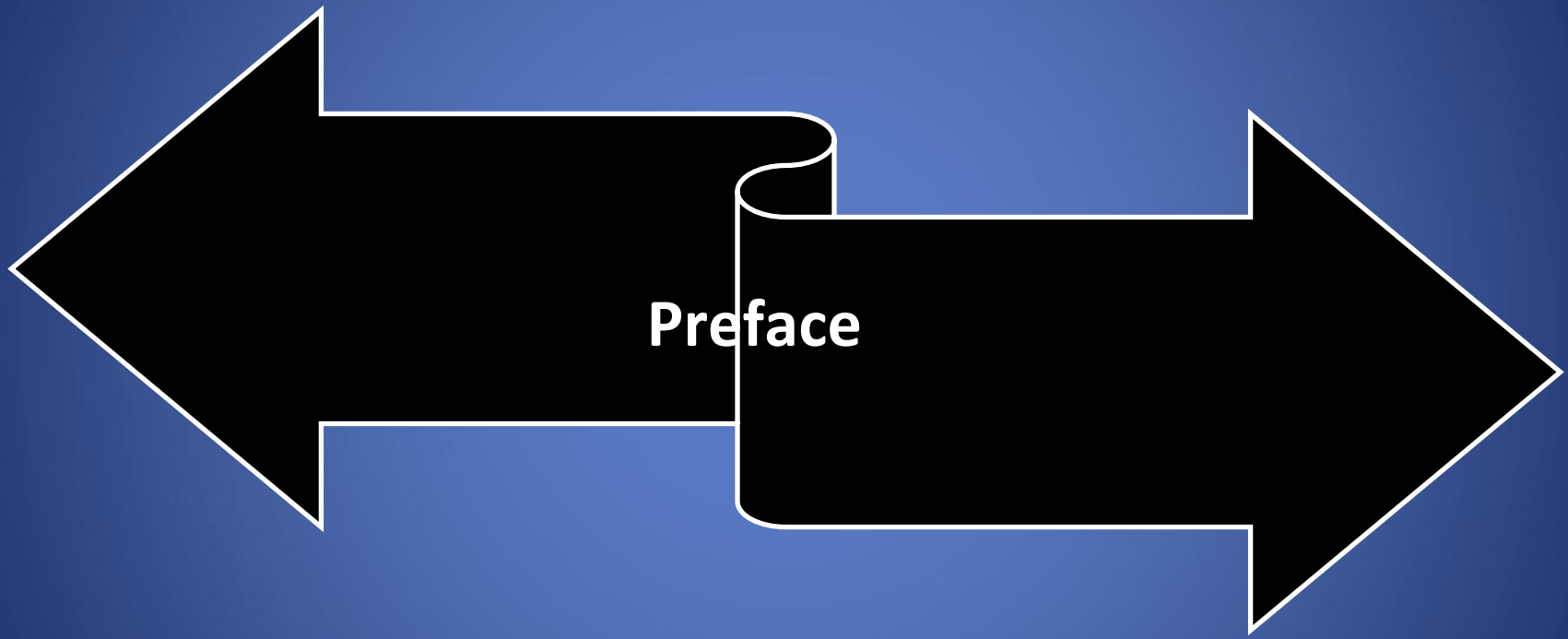
Dual Use Research of Concern

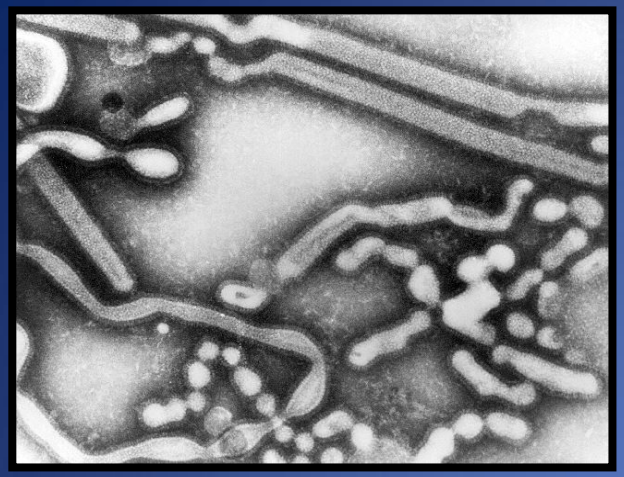
*promoting understanding * cultivating responsibility*

About this educational tool:

This is an introduction to dual use research of concern. It is offered as a tool for achieving several interrelated purposes, including promoting discussion, increasing awareness, and cultivating responsibility for dual use research of concern. It is just one of several available tools for educating individuals and groups about the challenges presented by life sciences (and related) research that may have both beneficial and malicious applications.

***Dual Use Research of Concern: Promoting Understanding + Cultivating Responsibility* has been designed for adaptation to the needs of different learners. In part or in whole, it can be used for self-directed learning by individuals or for learning and discussion by groups.**


Preface



In 1918, World War I ended,
but a pandemic of influenza, which
began in 1917 and ended in 1920, was
at its height.

Its impact, in terms of morbidity and mortality,
was and remains unprecedented.
At least 50 million people, 3 percent of
the world's population, died.
Approximately 500 million were infected.

These grim statistics account for the controversy
spawned by the reconstruction of the previously
extinct 1918 flu virus, reported in a paper
published by a group of investigators in *Science*
in October 2005*.

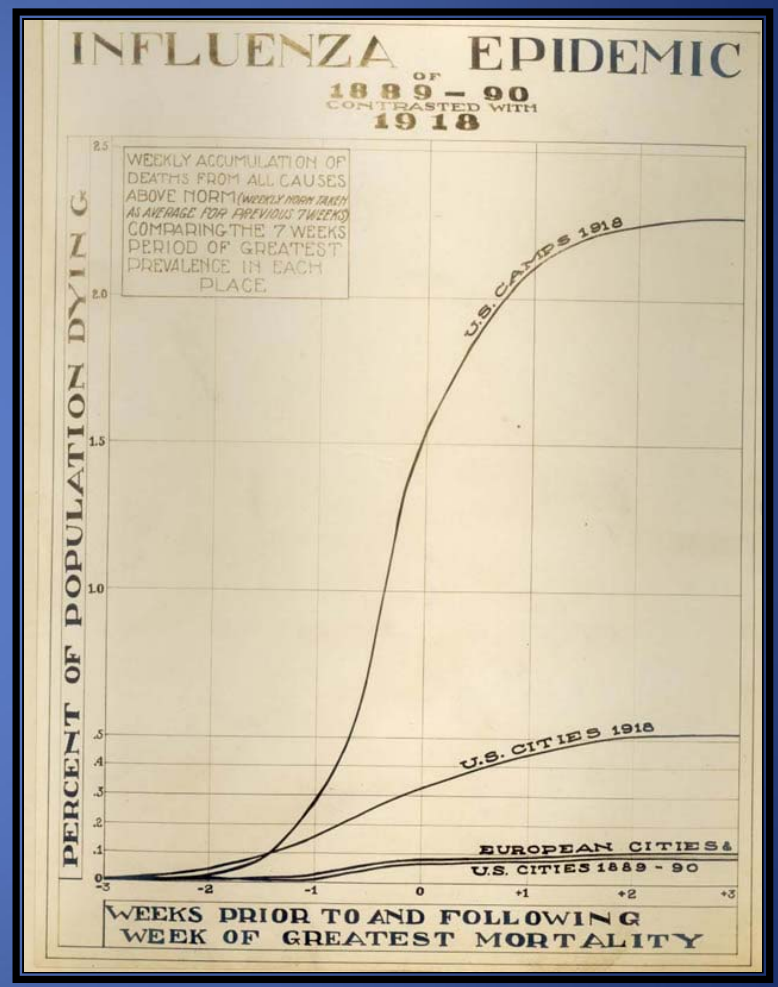
* T.M. Tumpey *et al* , Characterization of the Reconstructed 1918 Spanish Influenza Pandemic Virus, *Science* 310, 77 80 (2005).

In “Characterization of the Reconstructed 1918 Spanish Influenza Pandemic Virus,” Terrence M. Tumpey and his colleagues reported on their success in using “reverse genetics” to produce an influenza virus nearly identical to the 1918 pandemic virus.

Their aim was to study the extraordinary virulence of the virus. The results of such research could aid vaccine development efforts to protect the public against future pandemics or in the event of a future outbreak of a similarly pathogenic flu.

But, the research could be misused and put to malevolent purposes—for example, to reconstruct the virus and pose a threat to public health.

The research on the 1918 influenza virus vividly illustrates the dilemmas that can arise with the conduct and publication of ***dual use research***.



DUAL USE RESEARCH OF CONCERN

Promoting Understanding ▪ Cultivating Responsibility

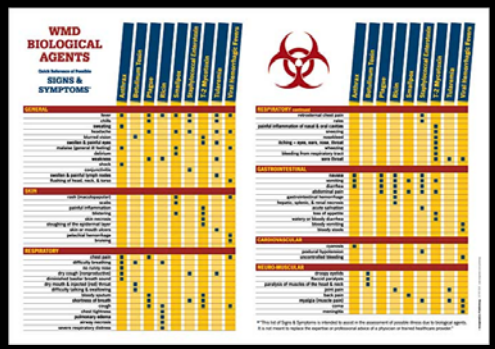
c o n t e n t s


An era of heightened concern
part 1

An era of heightened concern

The 1990s

A decade of mounting concerns about terrorism—including bioterrorism.



September 11, 2001

September 18, 2001

Letters containing spores of *Bacillus anthracis*, the causative agent of anthrax, were mailed to two U.S. Senators and several news media offices. Five people died; 17 others were infected.

1990s | 2000 | 2001

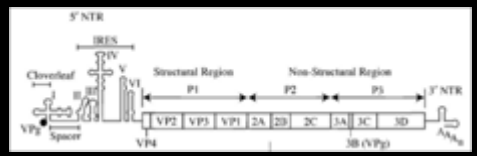
An era of heightened concern

2001

In the *Journal of Virology*, Australian researchers report that in re-engineering a mousepox virus, they unexpectedly produced a much more virulent virus—raising fears about the potential for bioterrorism.

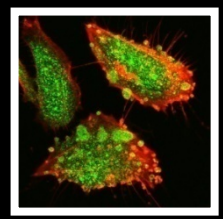
2002

In *Science*, investigators report that they have reconstructed the poliovirus from chemically synthesized oligonucleotides that were linked together and then transfected into cells.



2002

In *PNAS,* researchers report on their investigations into the immune response to a virulence gene from vaccinia, including information on how to increase viral virulence.



2001 → **2002**

An era of heightened concern

2004

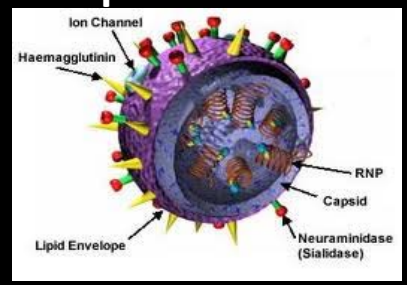
The National Research Council publishes the Fink Report recommending that scientists be educated about their responsibilities with regard to dual use research.

2004

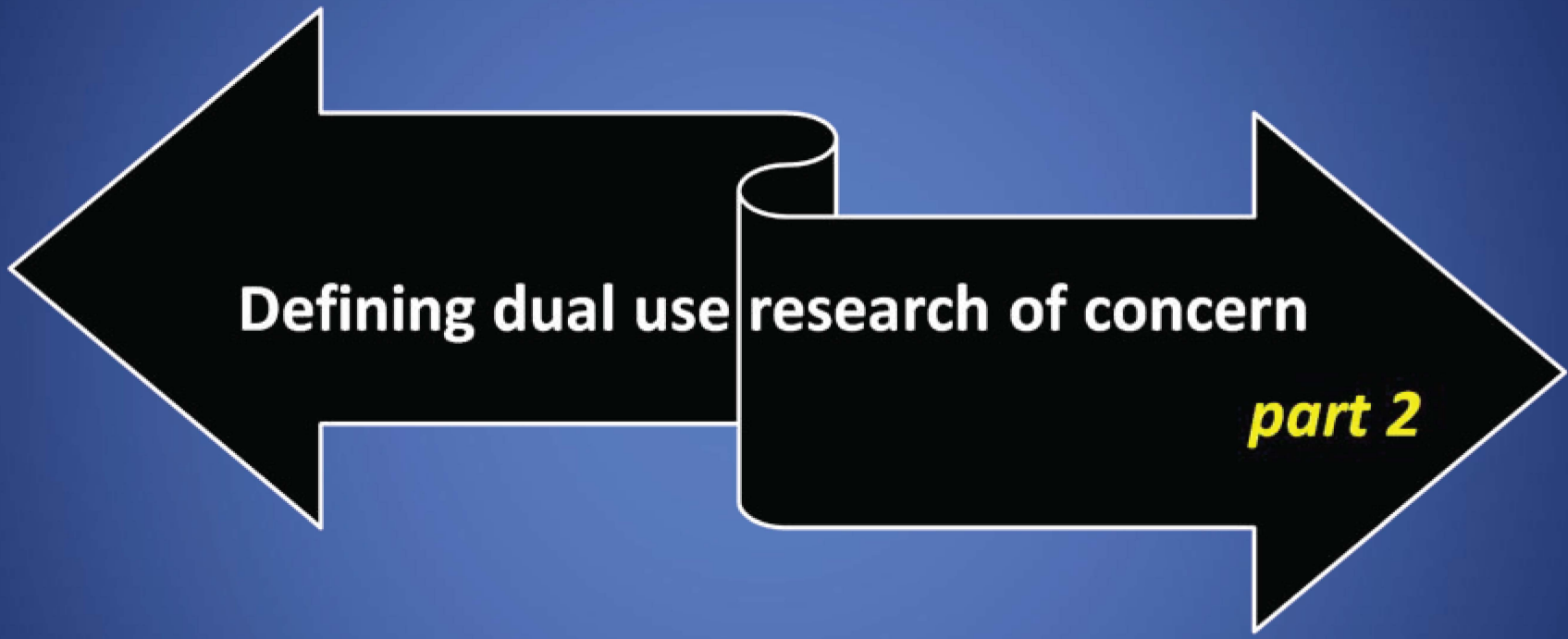
The National Science Advisory Board for Biosecurity is established to provide advice, guidance, and leadership regarding biosecurity oversight of dual use research. Holds first meeting in 2005.

2005

In *Science,* researchers from the Centers for Disease Control and their colleagues report that they have successfully reconstructed the influenza virus that caused the 1918 flu pandemic.

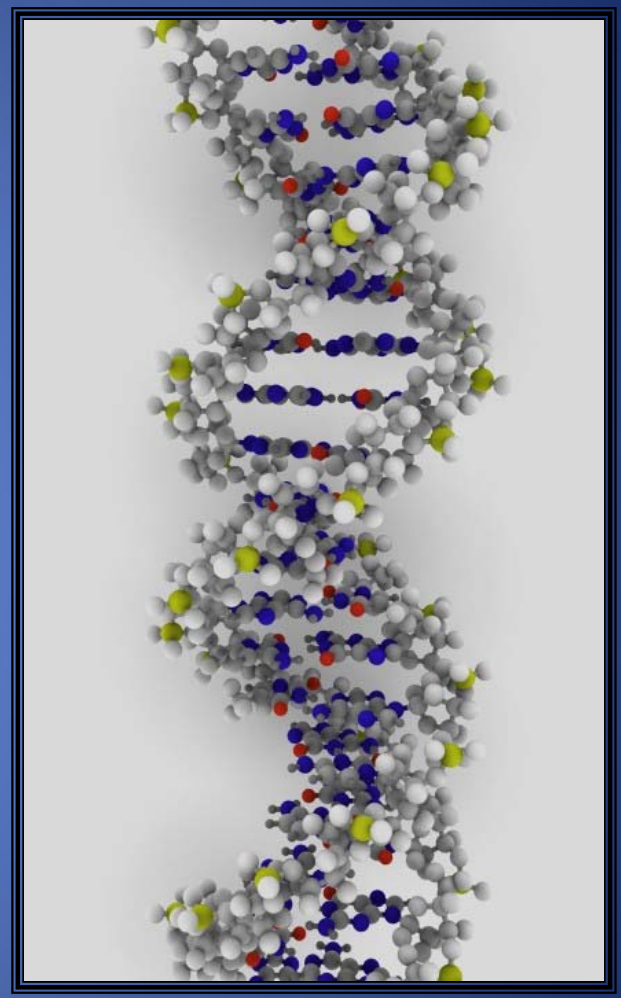


2004 → **2005**


Defining dual use research of concern
part 2

If dual use research is distinguished from other types of life sciences research ***by its potential for benevolent and malevolent application***, then few of the products of life sciences research—information or technologies—lack that potential.

The challenge: formulating a definition that enables identification of research warranting concern, vigilance, and perhaps oversight.



Dual use research of concern

A definition proposed by the National Science Advisory Board on Biosecurity

According to National Science Advisory Board for Biosecurity (NSABB), dual use research of concern is "[R]esearch that, based on current understanding, can be reasonably anticipated to provide knowledge, products, or technologies that could be directly misapplied to pose a threat to public health and safety, agricultural crops and other plants, animals, the environment, or materiel."*

* Established in 2005, the NSABB is a Federal advisory committee chartered to provide advice, guidance, and leadership regarding biosecurity oversight of dual use research to all Federal departments and agencies with an interest in life sciences research. The NSABB advises on and recommends specific strategies for the efficient and effective oversight of federally conducted or supported dual use biological research, taking into consideration national security concerns and the needs of the research community. The definition of dual use research is from the NSABB's 2007 report, *Proposed Framework for the Oversight of Dual Use Life Sciences Research: Strategies for Minimizing the Potential Misuse of Research Information.*

The NSABB has identified 7 categories of research that might qualify as dual use research of concern and should therefore receive closer scrutiny during its design, conduct, and perhaps publication. *These include research that might*

1. **Enhance the harmful consequences of a biological agent or toxin.**

   Example: Information on how to make a seasonal strain of the influenza virus as deadly as the 1918 pandemic strain.

2. **Disrupt immunity or the effectiveness of an immunization without clinical and/or agricultural justification.**

   Example: information on the insertion of an immunosuppressive cytokine into a viral genome to render the antiviral immune response less effective.

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7 categories of research that might qualify as dual use research of concern—research that might

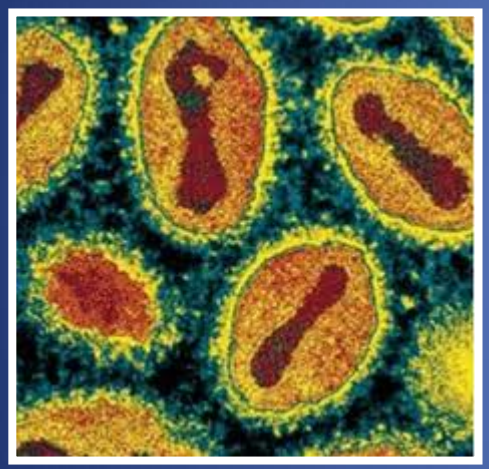
Staphylococcus aureus

3. Confer to a biological agent or toxin, resistance to clinically and/or agriculturally useful prophylactic or therapeutic interventions against that agent or toxin or facilitate their ability to evade detection methodologies.

Example: Information on how to confer doxycycline resistance to **Vibrio vulnificus** ***or antibiotic resistance to agriculturally relevant microbes, such as rendering*** **Erwinia amylovora** ***resistant to streptomycin.***

7 categories of research that might qualify as dual use research of concern—research that might

4. **Increase the stability, transmissibility, or the ability to disseminate a biological agent or toxin.**



Variola virus

Examples: information on changing genetic factors to increase transmissibility and altering the route of transmission or vector to increase the ease and effectiveness by which an agent may be transmitted.

5. **Alter the host range or tropism of a biological agent or toxin.**

Example: Knowledge of how to convert nonzoonotic agents into zoonotic agents, altering the tropism of viruses, and expanding the varieties of the same plant that a pathogenic agent could infect.

7 categories of research that might qualify as dual use research of concern—research that might

6. Enhance the susceptibility of a host population.

   Example: Information on how to create a stable recombinant Lactobacillus casei *that could effectively block the host's ability to synthesize an important immune signal, such as tumor necrosis factor alpha, which may directly facilitate the evasion of normal host defenses.*

7. Generate a novel pathogenic agent or toxin or reconstitute an eradicated or extinct biological agent .

   Examples: Information on how to construct a de novo *microbial pathogen using unique gene sequences or combinations of sequences that do not exist in nature; or on how to reconstitute a pathogen that no longer exists in nature, such as the 1918 pandemic influenza virus.*


Researcher responsibilities
part 3

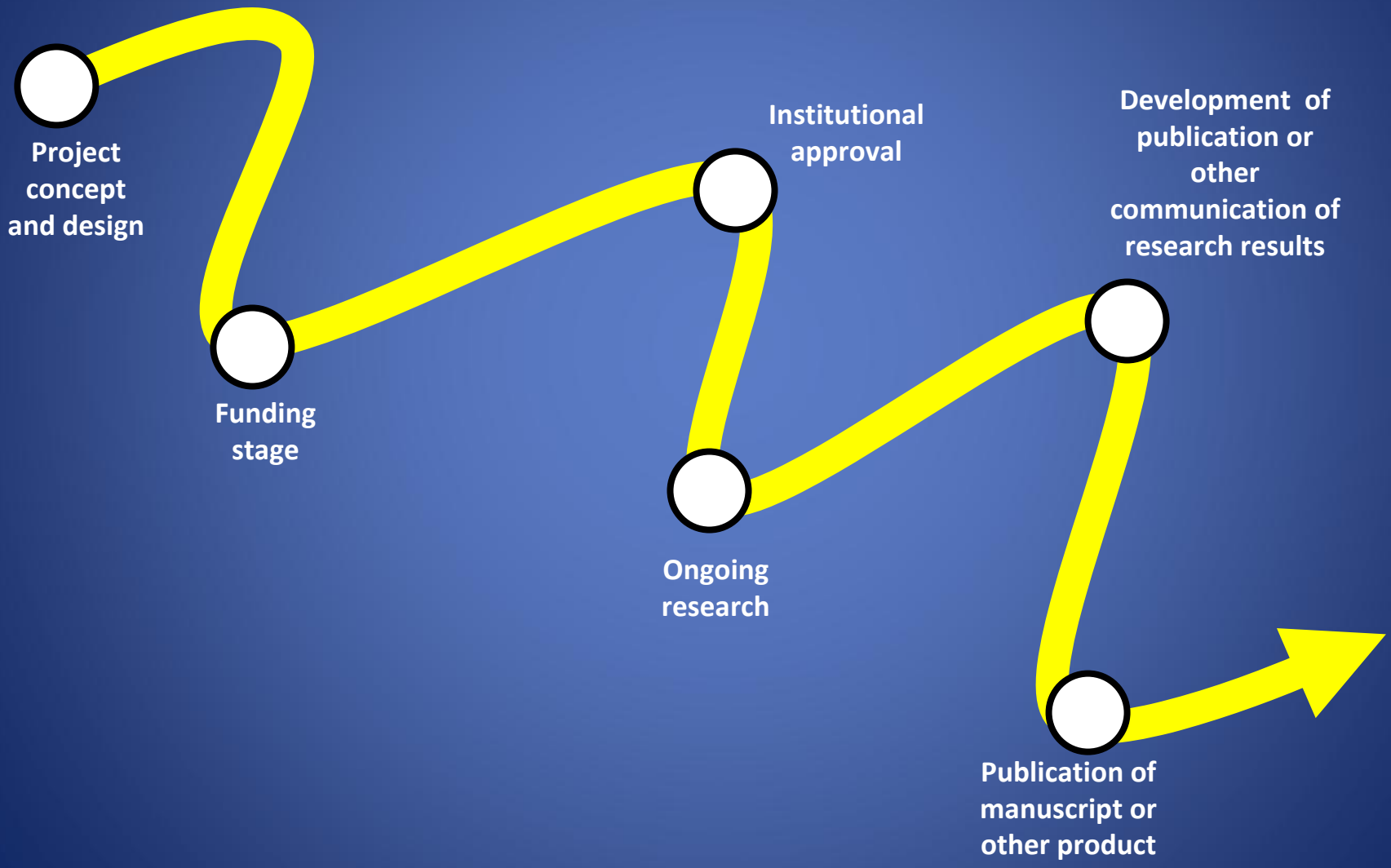
The responsible conduct of dual use research

The critical role of researchers

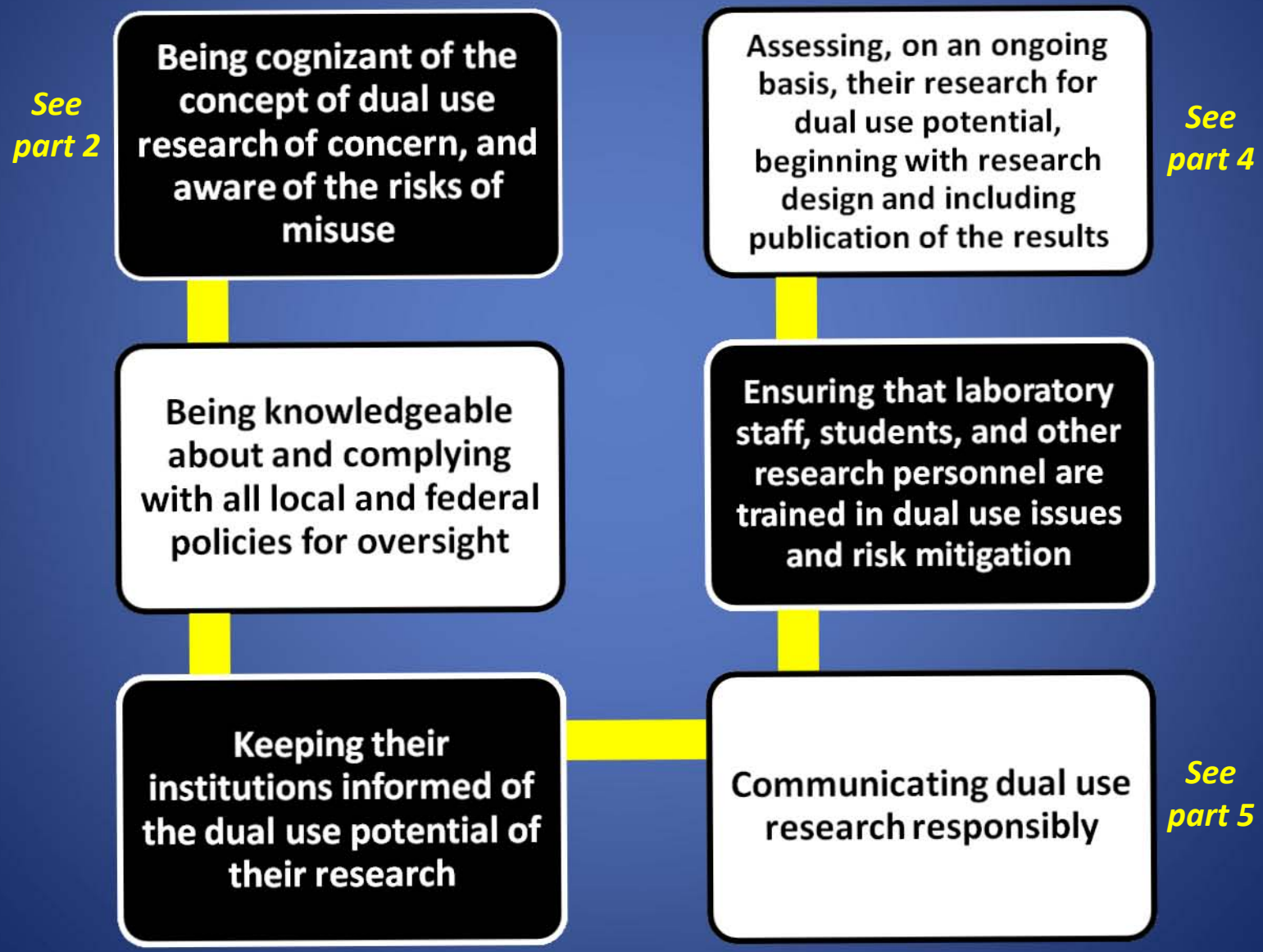
Although the responsible conduct of dual use research requires the active, thoughtful engagement of funding organizations, institutions, and others, the researchers themselves *can* and *must* play a central role …

… After all, they know their research best and are in the best position to anticipate the types of knowledge, products or technologies that might be generated, the potential for misuse, and the degree of immediacy of that threat.

Researcher responsibilities span the successive phases of the research process



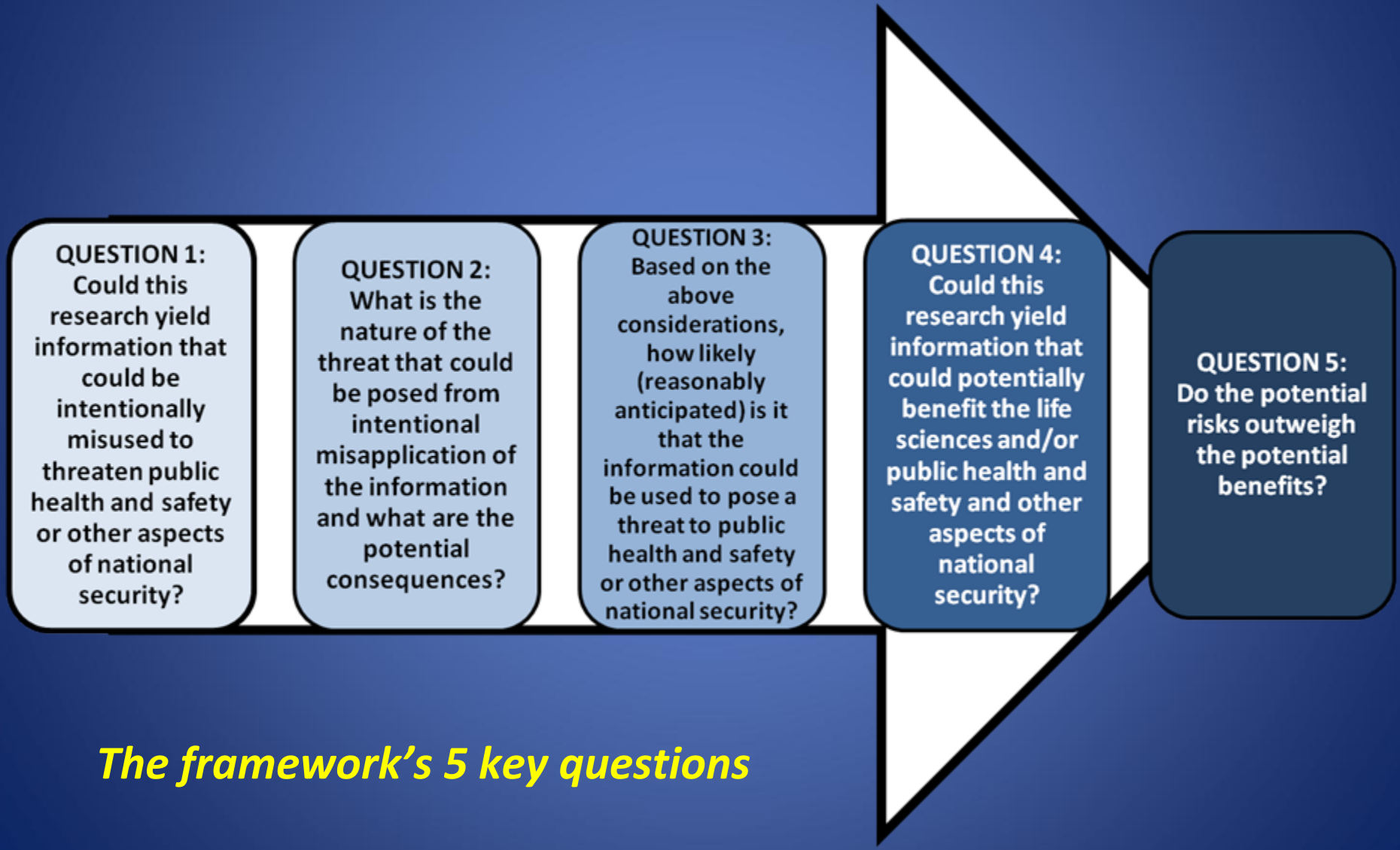
Researcher responsibilities




A framework for risk assessment
and management
part 4

Is this dual use research of concern?

A framework for assessing and managing risks



The framework's 5 key questions

Is this dual use research of concern?

A framework for assessing and managing risks

1. Could this research yield information that could be intentionally misused to threaten public health and safety or other aspects of national security?

- **What is the nature of the information? Is it novel?**
- **Is the information applicable to other, perhaps common organisms, biologics, etc.?**
- **Could the information be directly misused to pose a threat? Does the information need to be combined with other information to pose a threat? If so, is that other information already available?**

Is this dual use research of concern?

A framework for assessing and managing risks

2. What is the nature of the threat that could be posed from the intentional misapplication of the information and what are the potential consequences?

- **What is the potential nature (e.g., economic, agricultural, public health) and what is the potential impact of the threat?**
- **What is the scope of the potential threat (e.g., how many/which people, plants, animals might be adversely affected)?**
- **Are there currently countermeasures for this threat?**
- **What type of technical expertise and/or physical resources would be needed to apply the information for malevolent purposes?**
- **In what timeframe might the information be misused? Is there concern about immediate or near-future potential use, or is the concern about misuse in the distant future?**
- **Would it require a low or high degree of technical skill and sophistication to use the dual use information for harmful purposes?**

Is this dual use research of concern?

A framework for assessing and managing risks

3. Based on the preceding considerations, how likely—reasonably anticipated—is it that the information cold be used to pose a threat to public health and safety or other aspects of national security?

If there is NO discernable potential threat

Then, discontinue the analysis and proceed with the research but continue to be vigilant regarding dual use issues that may arise during the conduct of the research

If there IS a discernable potential threat

Then, proceed with the analysis

Is this dual use research of concern?

A framework for assessing and managing risks

4. Could this research yield information that could potentially benefit the life sciences and/or public health and safety and other aspects of national security?

- **If so, what is the nature of that information?**
- **What is the nature of the potential benefit?**
- **How much of a benefit might there be?**

Is this dual use research of concern?

A framework for assessing and managing risks

5. Do the potential risks outweigh the potential benefits?

- **If not, determine applicable risk management strategies.**
- **If so, consider whether the research should be modified, conducted at a later time when the benefits outweigh the risks, or delayed (perhaps, in rare cases, even discontinued).**
- **The risk/benefit assessment should be conducted periodically.**


Communicating dual use research of concern
part 5

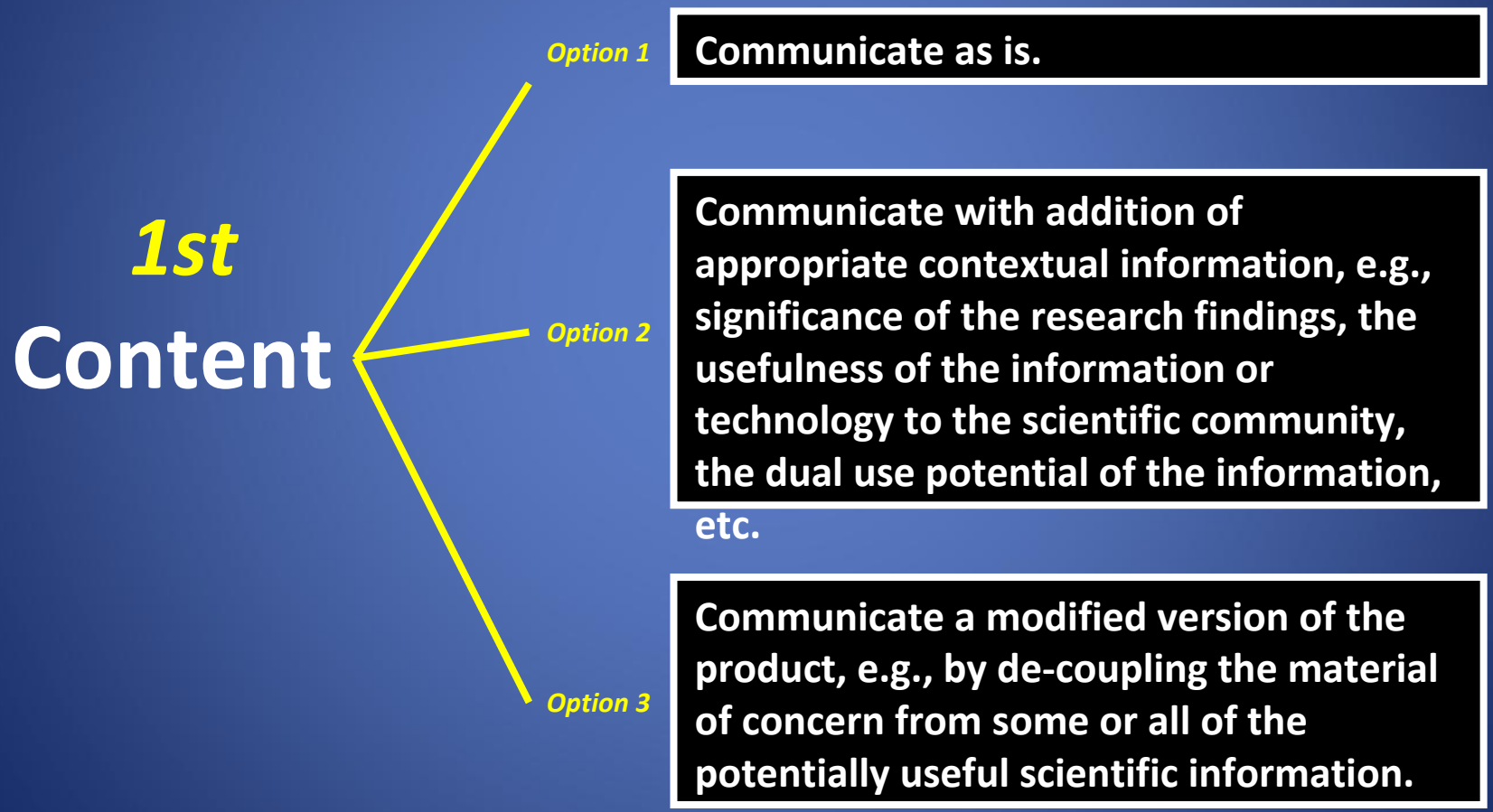
Decisions about the responsible communication of research with dual use potential should address the following in sequence:

1) **Content**

2) **Timing**

3) **Extent of distribution**

Dual use research of concern potential: *Communication decisions*



Dual use research of concern potential : *Communication decisions*

2nd

Timing

Option 1 **Communicate immediately.**

Option 2 **Defer communication until a clearly defined and agreed-upon endpoint is reached, e.g., a condition is met such that communication no longer poses the same degree of risk.**

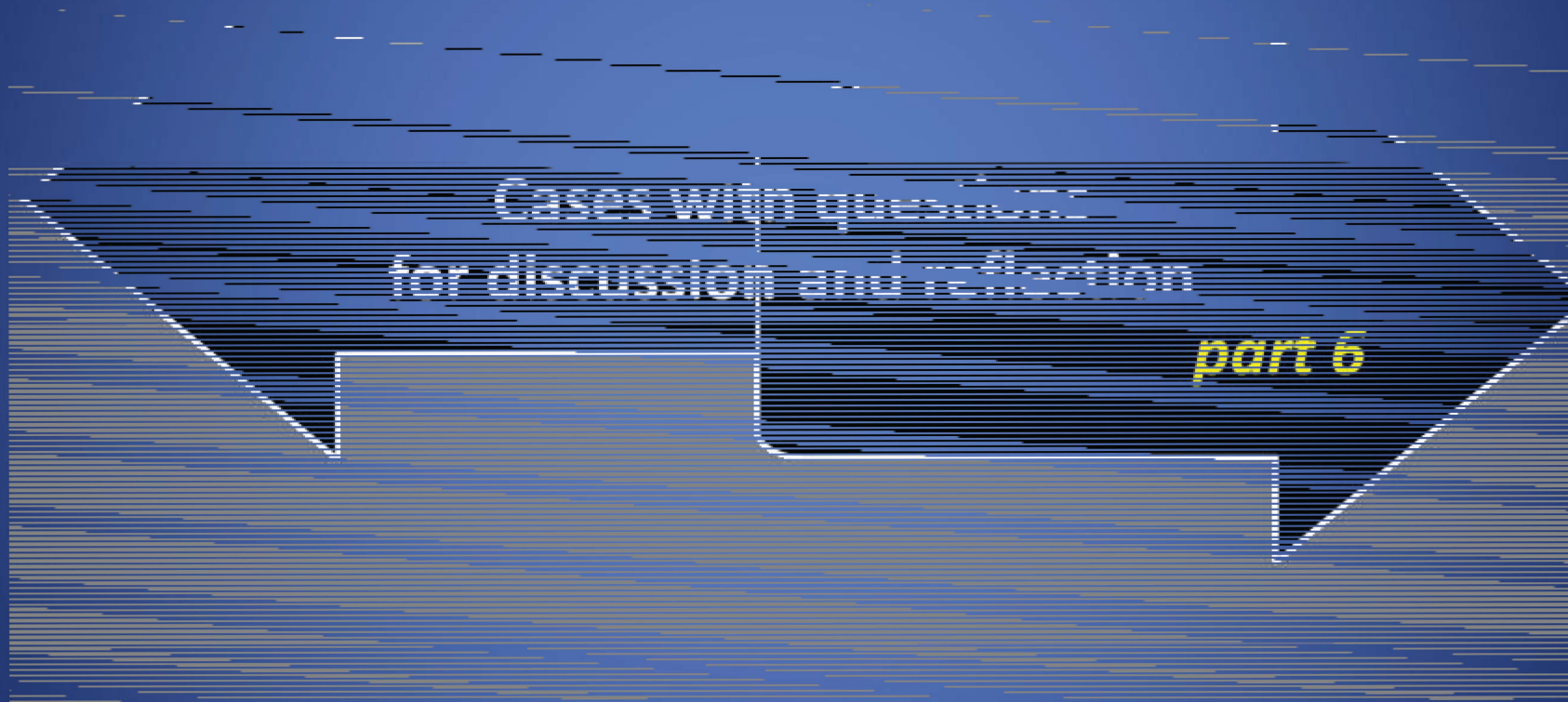
Dual use research of concern potential : *Communication decisions*

3rd Extent of Distribution

Option 1 — Do not limit distribution.

Option 2 — Limit access to selected individuals on a "need to know" basis. (Thus, with this option, it would be necessary to identify categories of individuals who should have access and under what circumstances.)

Option 3 — Do not publish the product or otherwise make it accessible to the public.

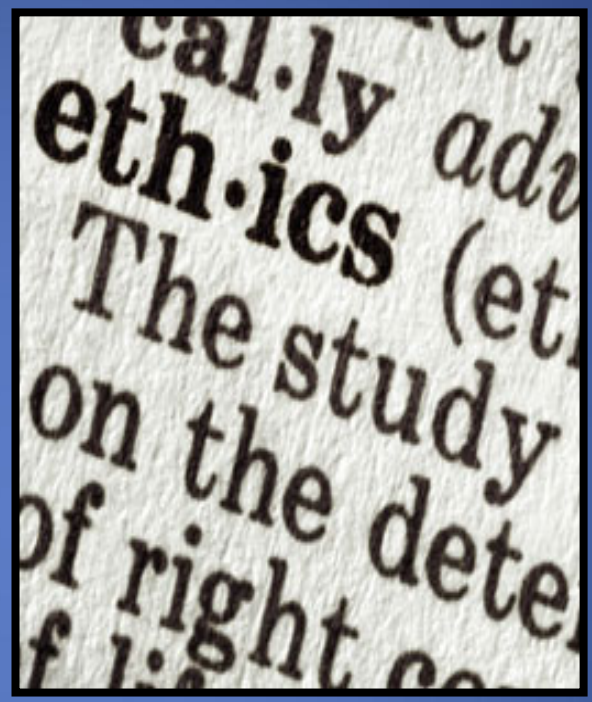

Cases with questions
for discussion and reflection
part 6

There are several strategies for raising awareness about, and inculcating responsibility for dual use research of concern.

For example, some professional
cieties have developed codes of conduct for dual use research of concern.

To facilitate the consideration, formulation, and dissemination of such a code, the NSABB has developed a Codes of Conduct Toolkit, available at: [web address]

Educational
interventions
targeted at
students
and investigators
in the life sciences
are crucial
to raising awareness
and inculcating responsibility.



Case-based interventions use real or realistic scenarios to challenge groups and individuals to wrestle with the dual use dilemma and reason through the question of

What should you do?

in every phase of the dual use research process.

The cases:
Objectives for learning and discussion

- Demonstrate an understanding of the dual use dilemma, including "real life" and hypothetical examples of dual use research
- Demonstrate an ability to identify aspects and products of research with the potential for misuse
- Demonstrate an understanding—and ability to formulate—workable strategies for minimizing the risk of misuse
- Delineate responsibilities and define appropriate conduct when designing, conducting, and communicating dual use research

1. Before the Study: Using Adenovirus

Sonia is a doctorate student who is developing a new project in which she plans to test a gene transfer technique to treat colon cancer tumors. The technique uses a modified adenovirus as a vector. It modifies the adenovirus in such a way that it specifically targets colon carcinoma cells and can be used to deliver tumor suppressor genes with the aim of overcoming the mutated genes that are implicated as the cause of the tumors. Modified adenoviruses have been used as vectors for gene transfer before but with only partial success. Sonia's technique is an improvement on existing methods and promises to avert or resolve the problems that have hampered success in the past. Moreover, the method is easy to use and relatively cheap. Although she has not published on the new method as yet, her colleagues have all tested it and are very impressed; indeed, they have encouraged her to patent the method.

1. Before the Study: Using Adenovirus

continued

Sonia's enthusiasm for her work, however, has been dimmed a bit by an off-handed comment by her colleague, Dan, who observed that the technique could be used to deliver toxins and other harmful agents to cause harm to animals, agriculture and perhaps even to humans. Now, Sonia is not sure what to do.

***Q:** Should Sonia disregard Dan's comment—after all, she is working on a possible treatment for cancer?*

***Q:** Should Sonia inform others about the potential for misuse of her newly developed method? If so, whom should she inform? Her colleagues? The editors and readers of the journal or journals in which she might publish her work?*

***Q:** Is there some other course of action that Sonia should consider?*

***Q:** Are there conditions under which research like Sonia's should be prevented from being carried out?*

2. During a Study:
Studying *Streptococcus Pneumoniae*

Ann, a post-doctoral fellow is working with Peter, a senior researcher, on a study of antimicrobial resistance in gram-positive pathogenic bacteria. Ann is studying recently isolated strains of *Streptococcus pneumoniae* that have developed antibiotic resistance and cause significantly increased pneumonia morbidity and mortality. She has identified a gene that she believes is responsible for the resistance, one that encodes part of a membrane-bound protein pump that removes materials from bacterial cells. And with that gene, she has created a variant with increased capacity that provides heightened resistance.

2. During a Study:
Studying *Streptococcus Pneumoniae*

continued

Q: ***This research has the clear potential to yield public health benefits, but it could also be used for malevolent purposes. What, if anything, should Ann and Peter do to minimize the risks of misuse of the research?***

Q: ***Should Ann and Peter be held responsible if the findings of their research are malignantly misused?***

3. The Editor's Point of View: Studying the Interaction between a Virus and the Human Immune System

Sue and David submit to a major virology journal a manuscript describing how the insertion of an immunosuppressive cytokine into Pithecine virus viral genome renders the antiviral immune response less effective. The manuscript has been read by many of their colleagues, all of whom agreed that the findings reported are significant and could lead to better understanding of the interactions between this virus and normal immune function.

Several days later, David receives a call from the journal editor, who tells him that the draft paper will undergo special review due to the 'dual use nature' of the research.

3. The Editor's Point of View: Studying the Interaction between a Virus and the Human Immune System

continued

When David informs Sue of his conversation with the editor, she is understandably very worried that the manuscript may not be accepted for publication as a result of this special review. While the paper is under review, she and David reflect on the new dual use research of concern review policies being adopted by journals to which they regularly submit.

3. The Editor's Point of View: Studying the Interaction between a Virus and the Human Immune System

continued

***Q:** What considerations should guide editorial decisions about the publication of manuscripts describing dual use research?*

***Q:** Who should be involved in reviewing the paper?*

***Q:** If a manuscript is to be published, what measures should editors take to minimize the potential for misuse?*

***Q:** If the paper is rejected due to its dual use potential, what, if anything, should be done to ensure that the paper is not published elsewhere?*

4. Conference Talk/Poster Session: Working with *Clostridium Botulinum* – Some Surprising Results

The bacterium *Clostridium botulinum* produces a toxin that causes about 150 cases of food poisoning a year in the United States. Bioterrorists could exploit several of its properties—it is accessible, easy to prepare in large quantities, and would be deadly if added to the food or water supply. To counteract the effects of such an attack, a research team screened a library of compounds with the potential to inhibit the activity of botulinum toxin to determine if they could be used therapeutically after an attack.

4. Conference Talk/Poster Session: Working with *Clostridium Botulinum* – Some Surprising Results

continued

During the studies, the group found a small molecule scaffold that strongly enhances the catalytic activity through an apparent increase in binding affinity—in fact, the compound enhanced the activity of the toxin up to fourteen-fold. This finding could yield both benefits and harms. In minute doses, botulium toxin is used to treat cerebral palsy, spasmodic dysphonia, and other conditions and this finding could make this use even more effective therapeutically. But the discovery could be put to misuse as well in ways that are both easy and frightening to imagine.

4. Conference Talk/Poster Session: Working with *Clostridium Botulinum* – Some Surprising Results

continued

Q: ***Should these researchers share the results of their research at a scientific conference? What considerations should inform a decision on whether to share the findings?***

Q: ***Are there ways to share findings while minimizing the risks of misuse?***

5. Dual Use of Concern in Another Lab – Cell-matrix Interaction and Tumor Growth and Metastasis

Dr. Gray is interested in cell-matrix interaction and its role in tumor growth and metastasis. She finds that membrane protein X is over-expressed in tumor cells and thinks that it may regulate cell adhesion and invasion. She hypothesizes that the N-terminal domain would make a good dominant-negative inhibitor and discovers that expressing this domain inhibits adhesion and kills tumor cells. To produce pure protein to use as a drug to treat cancer, Dr. Gray and her colleague Dr. White develop a bacterial expression-secretion system and are able to isolate the recombinant N-terminal domain from bacterial culture medium. They are excited to find that it kills tumor cells at remarkably low concentrations (0.1 µg/ml), and they name the recombinant fragment "N-statin." They show that it does not kill normal cells until they use 20-fold higher doses.

5. Dual Use in Another Lab – Cell-matrix Interaction and Tumor Growth and Metastasis

continued

Their findings show that exceptionally low doses are needed for an effective cancer drug, but they also have results that suggest that if taken orally, even low doses kill mice. Their work illustrates that apart from being a potential drug for cancer, N-statin could be very cheap rat/mouse poison, because the bacterial expression-secretion system provides an easy source of the material.

Dr. Gray and Dr. White share with you their new methods and findings which you find impressive--especially the potency of the biological drug candidate—but you worry that the method and the findings with respect to toxicity pose real risks with respect to dual use concerns and biosafety.

5. Dual Use in Another Lab – Cell-matrix Interaction and Tumor Growth and Metastasis

continued

Q: ***What should you do in this case? Should you alert the researchers? the IBC? Someone else?***

Q: ***Should the method and the findings be shared with others working in this area? And if so, should they be notified of the potential dual use of this research?***