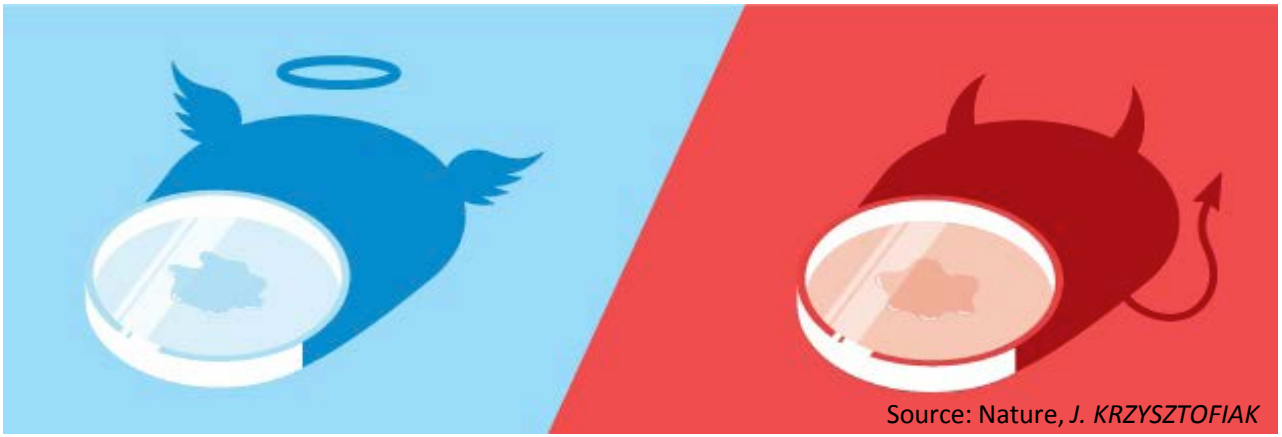
# Dual Use Research of Concern and the Debate about Gain-of-Function Studies

ABSA International
Grapevine, TX
October, 2016

JOE KANABROCKI, PH.D., SM(NRCM)
ASSOCIATE VICE-PRESIDENT FOR RESEARCH SAFETY
PROFESSOR OF MICROBIOLOGY
UNIVERSITY OF CHICAGO

# The “Dual Use” Dilemma



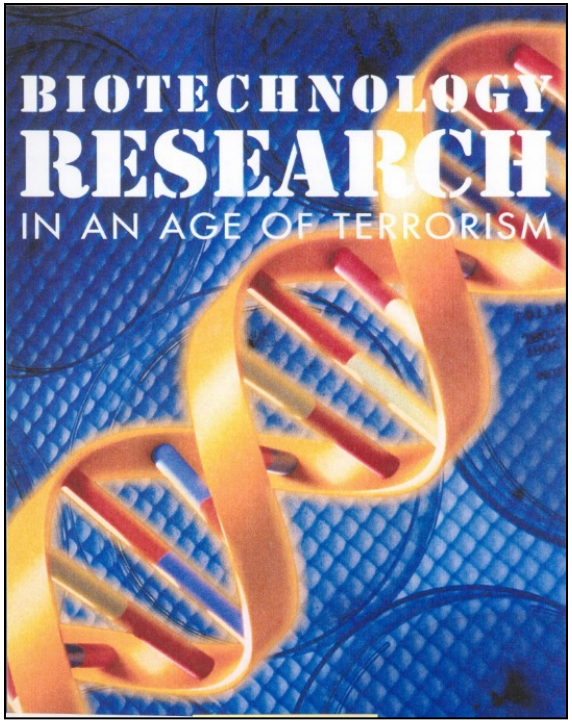

**Legitimate life sciences research can be used for both benevolent and malevolent purposes**

**Key Question:** How do you facilitate beneficial, life-saving biological research while mitigating the risks of misuse?

# The “Dual Use” Dilemma

**U.S. National Academies report *Biotechnology Research in the Age of Terrorism (2004)***

*Biotechnology represents a “dual use” dilemma in which the same technologies can be used legitimately for human betterment and misused for bioterrorism*



# National Science Advisory Board for Biosecurity (NSABB)

- U.S. government-wide initiative
- Federal Advisory Committee established in 2004
- Up to 25 voting members
- Broad scientific expertise as well as expertise in biosafety, biosecurity, risk communication, law, ethics, and more
- Non-voting *Ex Officio* members from Federal Agencies

*"…to provide, as requested, advice, guidance and leadership regarding biosecurity oversight of dual-use research, defined as biological research with legitimate scientific purpose that may be misused to pose a biological threat to public health and/or national security."*

*--NSABB Charter*

# Topics Addressed by NSABB

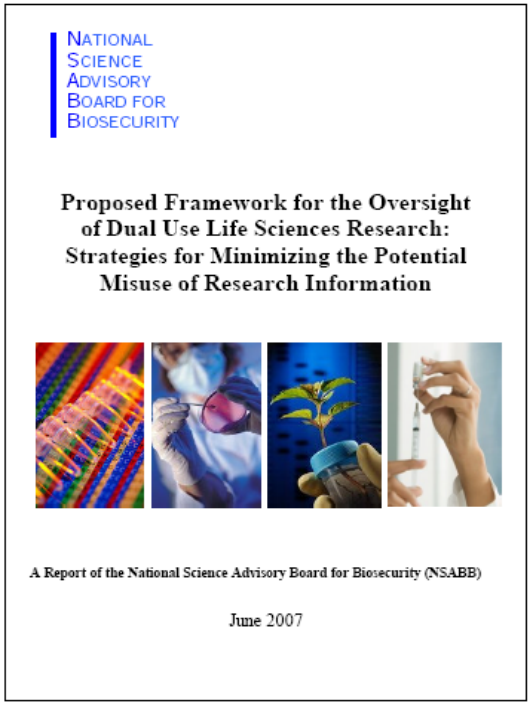
- Recommended national **guidelines for oversight** of dual use research at both local and federal levels
  - **Criteria for identifying** dual use research of concern
  - **Guidelines on communicating and disseminating** dual use research methodology and research results
  - A **code of conduct** for scientists and laboratory workers in life sciences research
- Developed a strategy for **biosecurity education and training** for all scientists and laboratory workers at federally funded institutions
- Promoted **international dialogue** on dual use research issues
- Other issues as assigned (synthetic genomics, personnel reliability, synthetic biology, GOF studies, occasional manuscript review)

# DUR vs. DURC

**Dual use research (DUR)** = legitimate research that yields information or technologies that could be misused for malevolent purposes

- **NOTE:** Most life sciences research conceivably could be considered DUR in that it has *some* potential to generate information that could be eventually misused

Goal is to identify the subset that has highest potential for generating information that could be readily misused = **DUR *of concern* (DURC)**



# U.S. DURC Policies

**The U.S. Government has issued two complementary policies for the oversight of life sciences DURC**

1. **USG Policy for Oversight of Life Sciences DURC (2012)**
   - Describes the role of the Federal funding agencies in identifying DURC and implementing risk mitigation strategies as necessary

2. **USG Policy for Institutional Oversight of Life Sciences DURC (2014)**
   - Focuses on the responsibilities of research institutions in identifying DURC and mitigating risks at the institutional level

**http://www.phe.gov/s3/dualuse/**

# DURC Agents

| | | |
|---|---|---|
| Influenza A H5N1 (HPAI) | **Ebola virus** | ***Francisella tularensis*** |
| Influenza A 1918 (reconstructed) | **Marburg virus** | ***Yersinia pestis*** |
| **Toxin-producing strains of *Clostridium botulinum*** | **Variola major virus** | ***Bacillus anthracis*** |
| **Botulinum neurotoxin** | **Variola minor virus** | ***Burkholderia mallei*** |
| **Foot-and-mouth disease virus** | **Rinderpest virus** | ***Burkholderia pseudomallei*** |

# The Gain-of-Function (GOF) Issue

**Gain-of-function** is a term used to refer to any modification of a biological agent that confers new or enhanced activity.

Debate has centered around **a specific subset of GOF studies** that involve the **generation of pathogens with pandemic potential**

- Studies that generate certain pathogens with enhanced pathogenicity or transmissibility (by respiratory droplets) in mammals
- The GOF studies that have raised concerns are often cited as an example of DURC
- Ongoing debate about risks and benefits

# GOF Studies: Benefits and Risks

**Potential Benefits of GOF Studies**

- Help define the fundamental nature of human-pathogen interactions
- Enable assessment of the pandemic potential of emerging infectious agents
- Inform public health and preparedness efforts
- Further medical countermeasure development

**Potential Risks of GOF Studies**

- Involve generating novel engineered pathogens that could pose a pandemic threat if they were to be accidentally or intentionally released
- May generate information that could be misused to threaten public health or national security
- Risks would increase as more labs perform this type of research

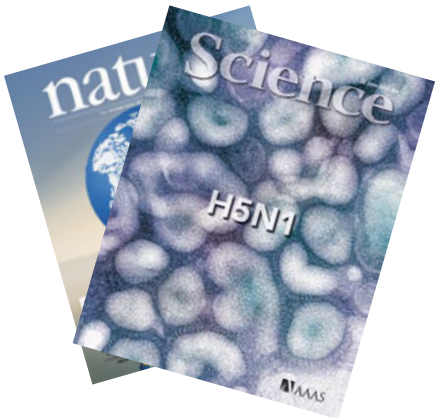
# H5N1 Manuscripts Launch a Debate about GOF Studies

Avian influenza remains a global health threat

- Questions about whether and how avian influenza viruses could become transmissible among humans remain important to science and public health

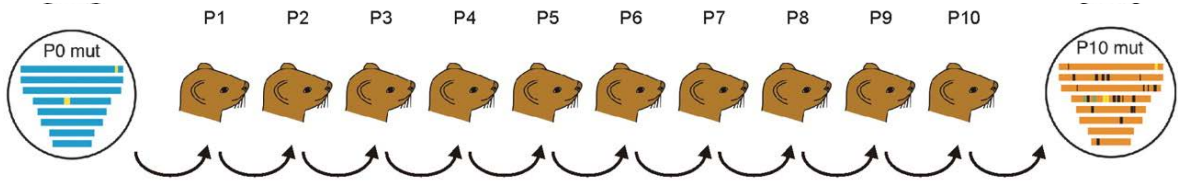
Two NIH-funded GOF studies generated highly pathogenic avian influenza H5N1 viruses that were transmissible by respiratory droplets among ferrets

- Confirmed that H5N1 had the potential to become mammalian transmissible
- Identified genetic determinants associated with mammalian-transmissibility of HPAI H5N1



# H5N1 Manuscripts Launch a Debate about GOF Studies

**Approach:** Rational mutagenesis and serial passaging




**Key Findings:**

- Demonstrated that HPAI H5N1 viruses could evolve to become transmissible between mammals by respiratory droplets
- Identified key amino acid residues that contribute to mammalian transmissibility
- Identified a number of mutations that have been observed in naturally-occurring strains

*Herfst et al. Science, Vol. 336 Issue 6088*

# H5N1 Manuscripts Launch a Debate about GOF Studies

The INDEPENDENT

Alarm as Dutch lab creates highly contagious killer flu

Some scientists are questioning whether the research should ever have been undertaken in a university laboratory, instead of at a military facility

Los Angeles Times

Fear Gone Viral

Despite government alarm bells, recent research with ferrets didn't create flu strains that threaten the world… there's really not much cause for alarm

The New York Times

An Engineered Doomsday

…the research should never have been undertaken because the potential harm is so catastrophic

nature

Don't censor life-saving science

Controlling who is allowed access to information about mutations in the H5N1 bird flu virus is unacceptable

# GOF Studies Raise Biosafety and Biosecurity Concerns

- **Dual use/biosecurity issues:** Do the studies generate information that could be utilized to create a potentially human-transmissible virus that, in the wrong hands, could be intentionally released to threaten public health and security?

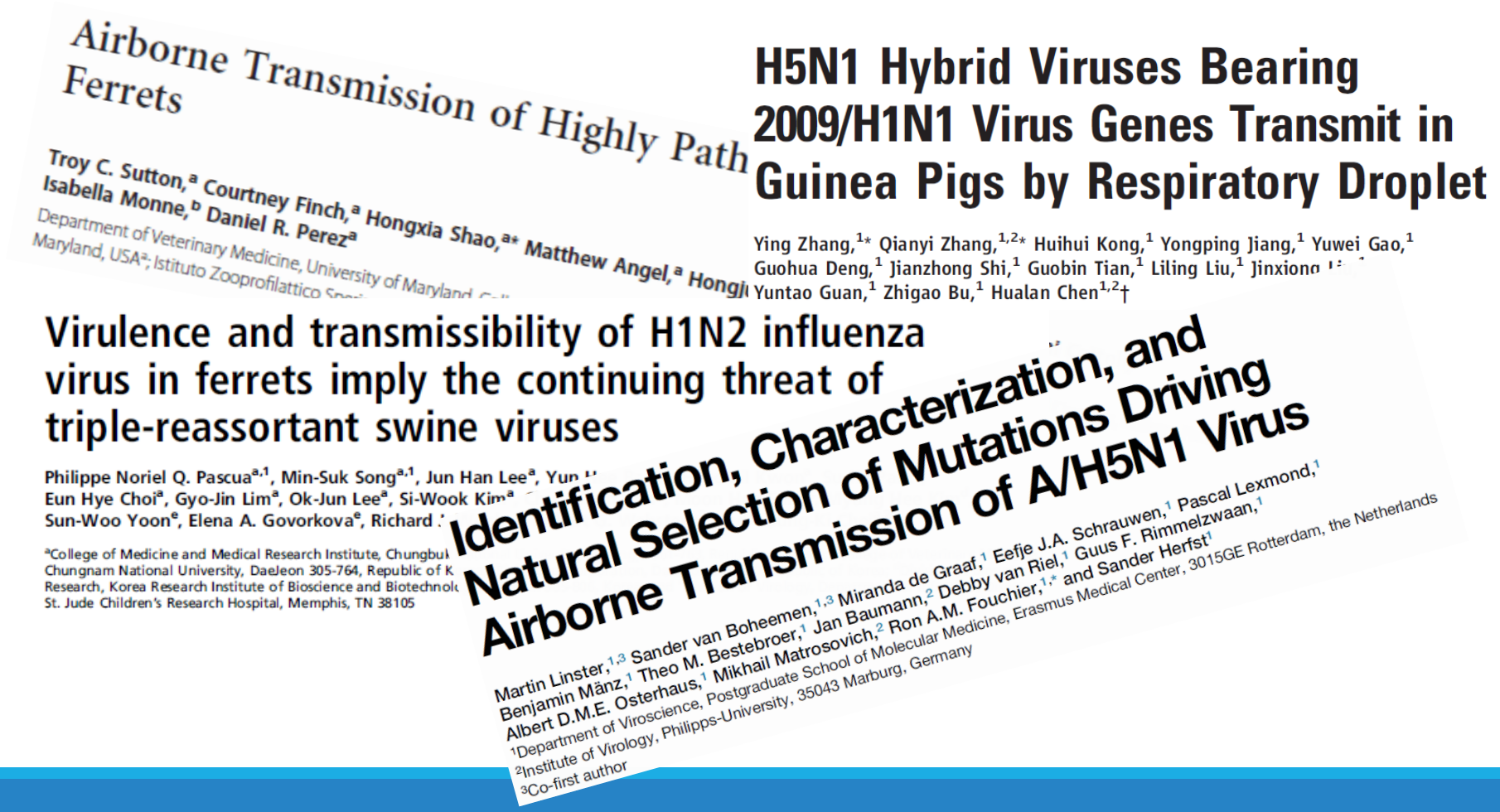
- **Biosafety issues:** Could the engineered pathogens accidentally infect a lab worker or be released into the environment?

***Should such research findings be communicated? If so, how can they be responsibly communicated?***

***Under what conditions can these studies be safely conducted?***

***Should this type of research be conducted at all?***

# H5N1 Manuscripts Published and GOF Studies Continue



# Debate about GOF Studies Continues

*For any experiment, the expected net benefits should outweigh the risks. Experiments involving the creation of potential pandemic pathogens should be curtailed until there has been a quantitative, objective and credible assessment of the risks, potential benefits, and opportunities for risk mitigation, as well as comparison against safer experimental approaches.*

***– Cambridge Working Group***

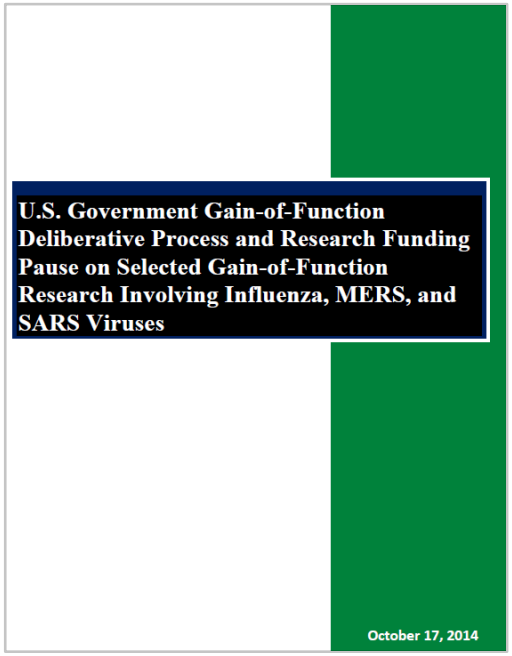
*If we expect to continue to improve our understanding of how microorganisms cause disease we cannot avoid working with potentially dangerous pathogens. In recognition of this need, significant resources have been invested globally to build and operate BSL-3 and BSL-4 facilities, and to mitigate risk in a variety of ways, involving regulatory requirements, facility engineering and training. Ensuring that these facilities operate safely and are staffed effectively so that risk is minimized is our most important line of defense, as opposed to limiting the types of experiments that are done.*

***– Scientists for Science***

# GOF Deliberative Process and Research Funding Pause

## Deliberative Process

In October 2014, the USG announced a process to re-evaluate the potential risks and benefits associated with GOF research involving pathogens with pandemic potential.




## Research Funding Pause

Deliberative process is accompanied by a pause in funding for projects that may be reasonably anticipated to generate influenza, MERS, or SARS viruses with enhanced pathogenicity and/or transmissibility in mammals via the respiratory route.

# The Charge to the NSABB

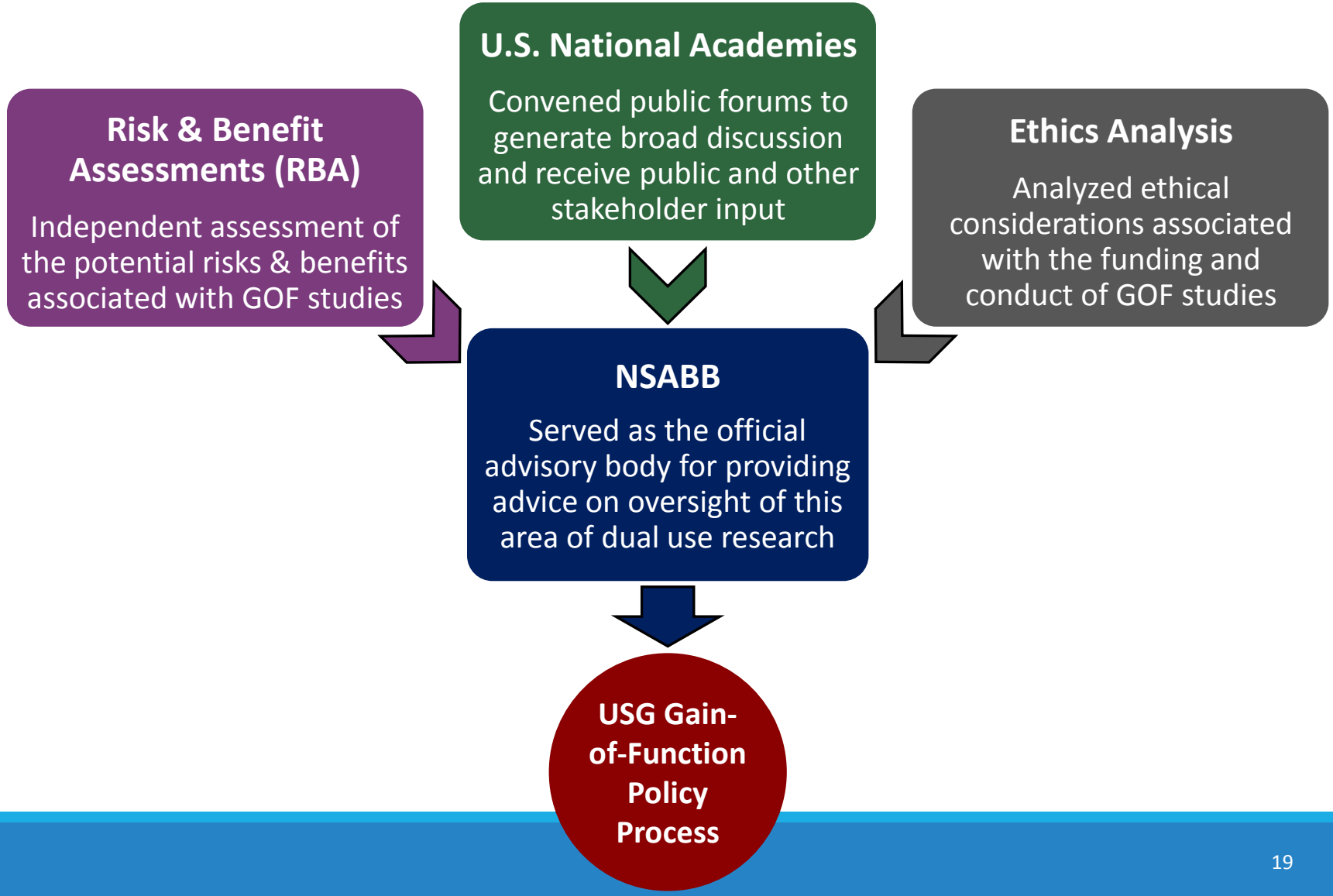
1. **Advise on the design, development, and conduct of risk and benefit assessments for GOF studies**

   - Framework for Conducting Risk and Benefit Assessments of Gain-of-Function Research (May 2015)

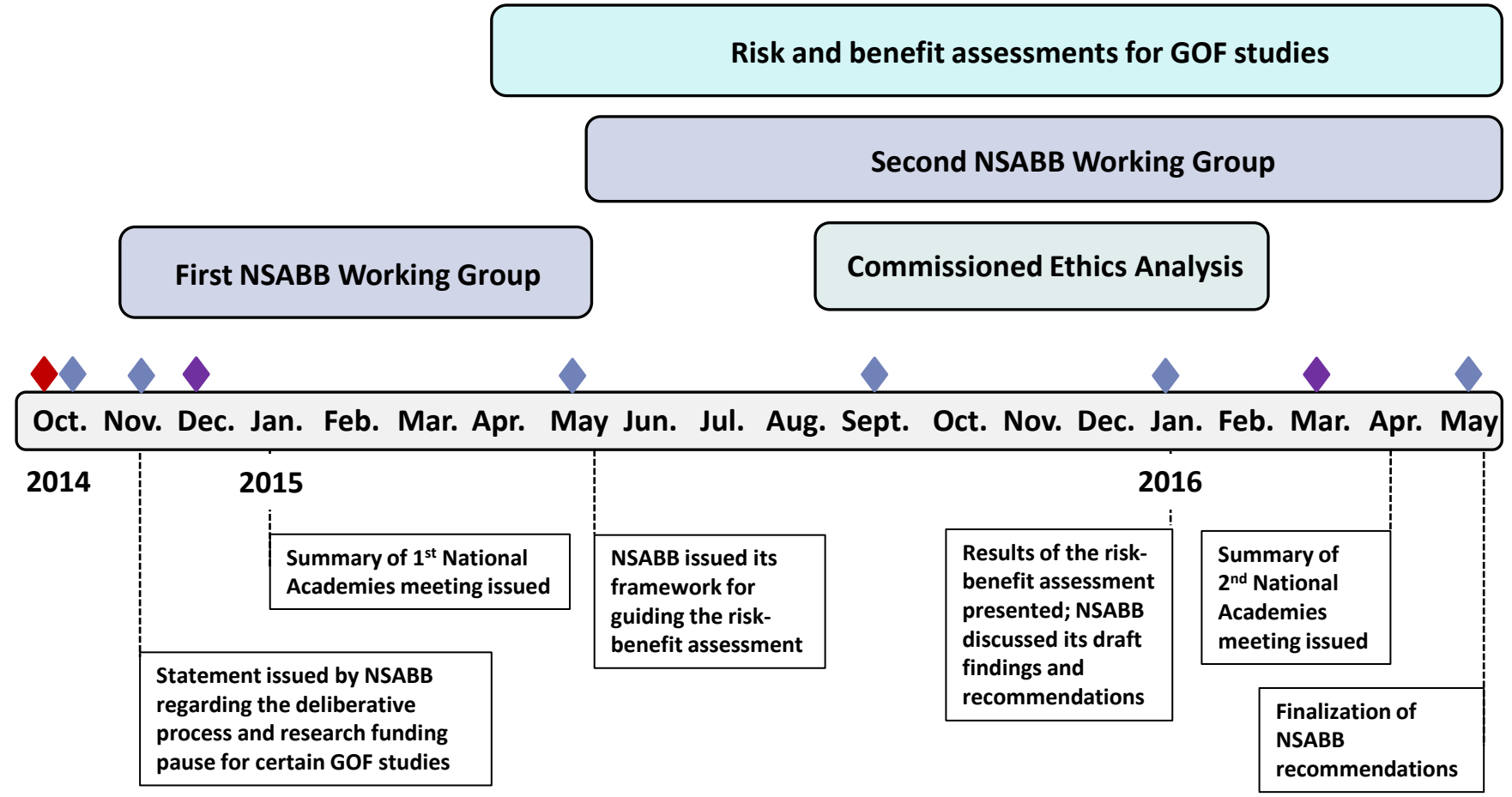
2. **Provide recommendations to the U.S. government on a conceptual approach to the evaluation of proposed GOF studies**

   - Draft Report: Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research (May 2016)

# GOF Deliberative Process



# Timeline of Major Events



# Stakeholder Perspectives Key to Deliberative Process

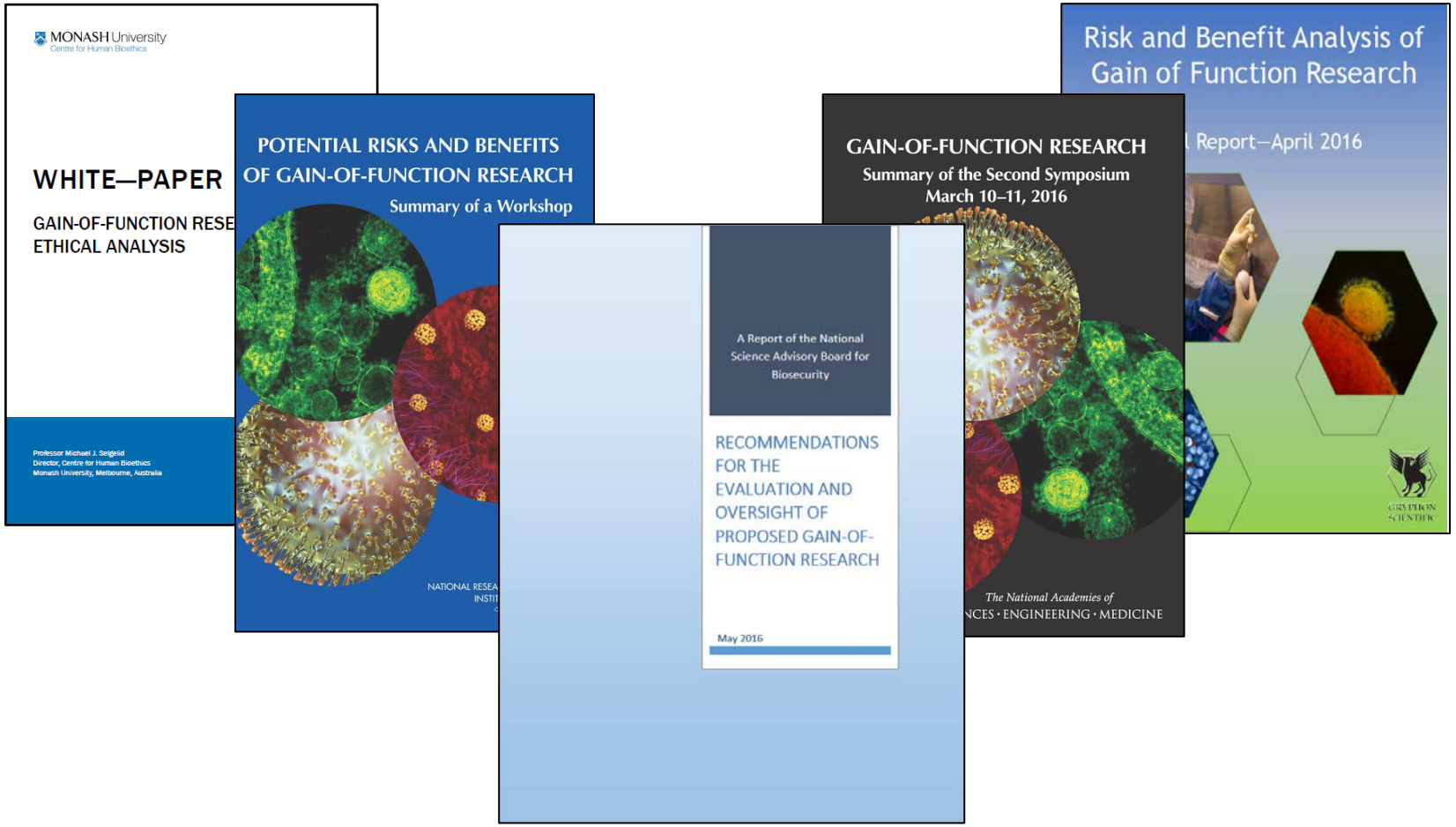
8 public meetings (6 NSABB; 2 National Academies)

95 invited speakers, presenters, and panelists

53 public commenters (written and oral)

56 experts interviewed by Gryphon for its Benefits Assessment

# GOF Deliberative Process – Analyses & Reports




http://osp.od.nih.gov/office-biotechnology-activities/biosecurity/nsabb

# NSABB Report on GOF Research

***Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research*** **(May 2016)**

- Guiding principles for NSABB deliberations
- NSABB's framework for conducting RBA
- Analysis and interpretation of the RBA
- Consideration of ethical values and decision-making frameworks
- Analysis of the current policy landscape and potential policy options
- Findings and Recommendations

# NSABB Report on GOF Research

*There are many types of GOF studies and not all of them have the same level of risks. Only a small subset of GOF research—**GOF research of concern (GOFROC)**—entail risks that are potentially significant enough to warrant additional oversight.*

*Research proposals involving GOF research of concern entail significant potential risks and **should receive an additional, multidisciplinary review, prior to determining whether they are acceptable for funding.** If funded, such projects should be subject to ongoing oversight at the federal and institutional levels.*

# Additional Pre-funding Review: Identifying GOFROC

**To be considered GOFROC, the research must, in a single step or over the course of multiple manipulations, be reasonably anticipated to generate a pathogen with both of the following attributes:**

1. **The pathogen generated is likely highly transmissible and likely capable of wide and uncontrollable spread in human populations.**
2. **The pathogen generated is likely highly virulent and likely to cause significant morbidity and/or mortality in humans.**

***For more description and examples see NSABB report p. 41-42 and Appendix C***

# Additional Pre-funding Review: Guiding Funding Decisions

**Only GOFROC projects that are in line with all of the 8 principles listed should be considered acceptable for funding.**

1. The research proposal has been evaluated by a peer-review process and determined to be **scientifically meritorious**, with high impact on the research field(s) involved.
2. The pathogen that is anticipated to be generated must be judged, based on scientific evidence, to be **able to arise by natural processes**.
3. An assessment of the overall potential risks and benefits associated with the project determines that the **potential risks as compared to the potential benefits to society are justified**.
4. There are **no feasible, equally efficacious alternative methods** to address the same scientific question in a manner that poses less risk than does the proposed approach.

# Additional Pre-funding Review: Guiding Funding Decisions

**Only GOFROC projects that are in line with <u>all</u> of the 8 principles listed should be considered acceptable for funding.**

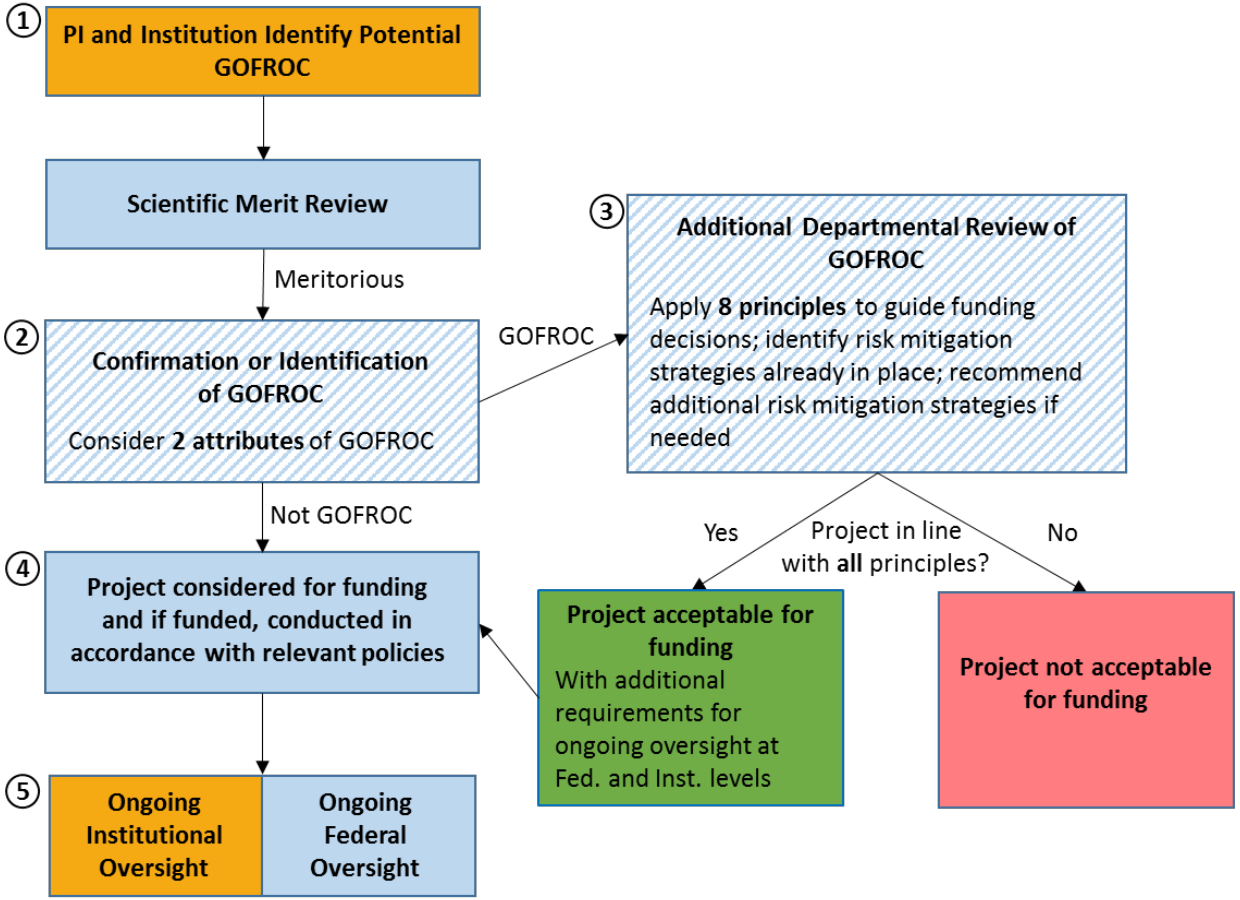
5. The investigator and institution proposing the research have the **demonstrated capacity and commitment to conduct it safely and securely**, and have the ability to respond rapidly and adequately to laboratory accidents and security breaches.

6. The **results of the research are anticipated to be broadly shared** in compliance with applicable laws and regulations in order to realize their potential benefits to global health.

7. The research will be supported through funding mechanisms that allow for appropriate **management of risks and ongoing federal and institutional oversight** of all aspects of the research throughout the course of the project.

8. The proposed research is **ethically justifiable**.

# Proposed Process: Review, Funding, & Oversight of GOFROC



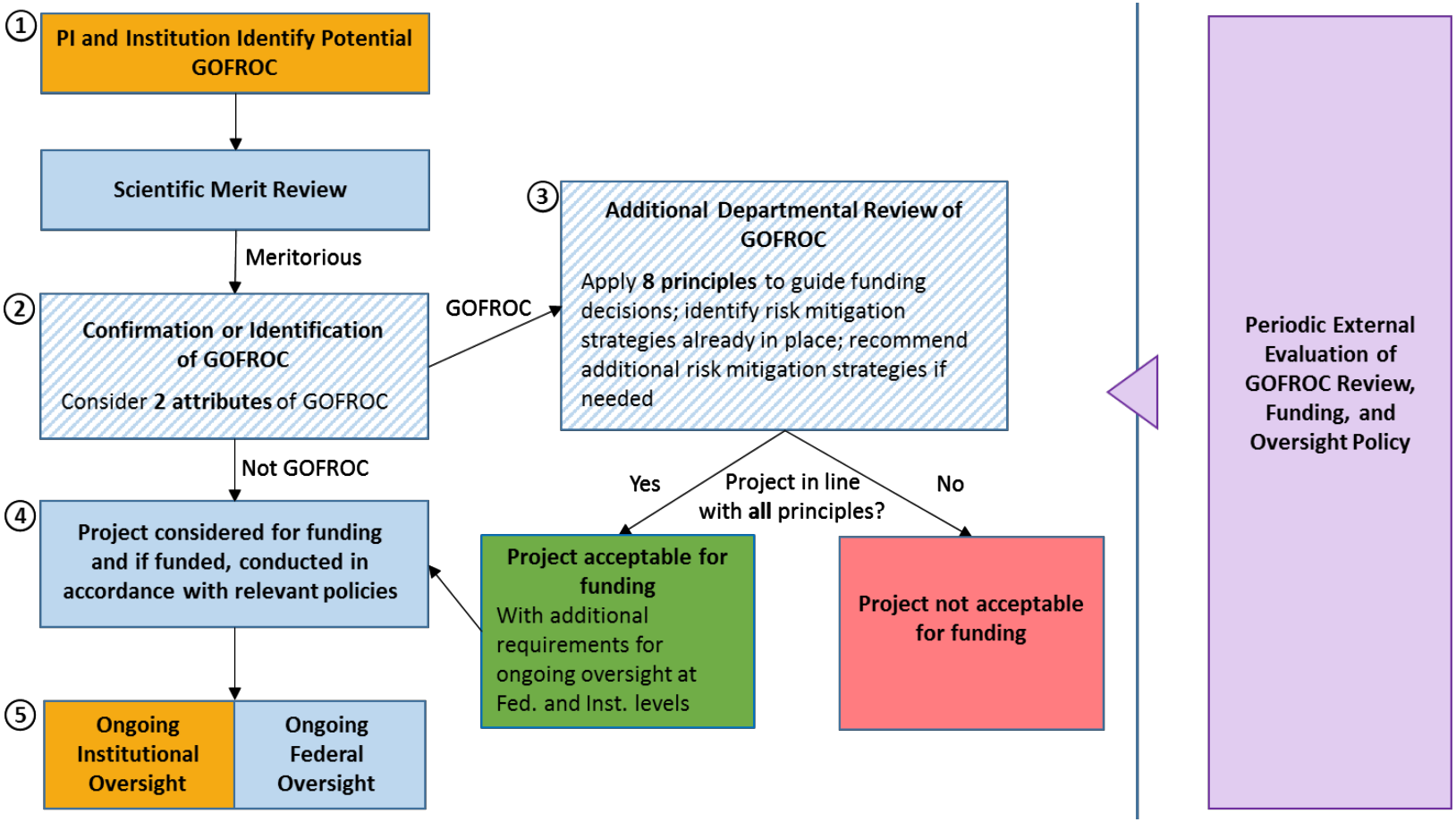



Research Institution | Federal Agency | Additional Federal GOFROC Review Mechanism

# Ongoing Oversight: Potential Risk Mitigation Measures

- Enhance biosafety practices or features, as warranted given the specific strains and proposed manipulations
- Enhance security measures around strains, reagents, notebooks, and personnel
- Prohibit certain additional GOFROC experiments without prior approval
- Treat the research as if subject to the USG DURC policies, if it is not already
- Identify certain experimental outcomes that would trigger a re-evaluation of the risks and benefits prior to proceeding with a study
- Communicate regularly and coordinate with federal, state, and local public health and safety officials on accident and theft response

# Periodic Evaluation of GOFROC Oversight Process




*NSABB Recommendation 2*

Research Institution | Federal Agency | Additional Federal GOFROC Review Mechanism | Federally-appointed Advisory Committee

# Other NSABB Recommendations

- **Pursue an adaptive policy approach** to help ensure that oversight remains commensurate with the risks
- Consider developing a system to **collect and analyze data** to help inform policy development
  - Laboratory safety incidents, near-misses, and security breaches
  - Institutional Review Entity challenges, decisions, and lessons learned
- Incorporate oversight mechanisms for GOF research of concern into **existing policy frameworks** when possible
- Consider ways to ensure that **all GOF research of concern** conducted within the U.S. or by U.S. companies is **subject to oversight, regardless of funding source**

# Other NSABB Recommendations

- Undertake broad efforts to **strengthen laboratory biosafety and biosecurity** and **seek to raise awareness** about the specific issues associated with GOF research of concern

- **Engage the international community** in dialogue about the oversight and responsible conduct of GOF research of concern

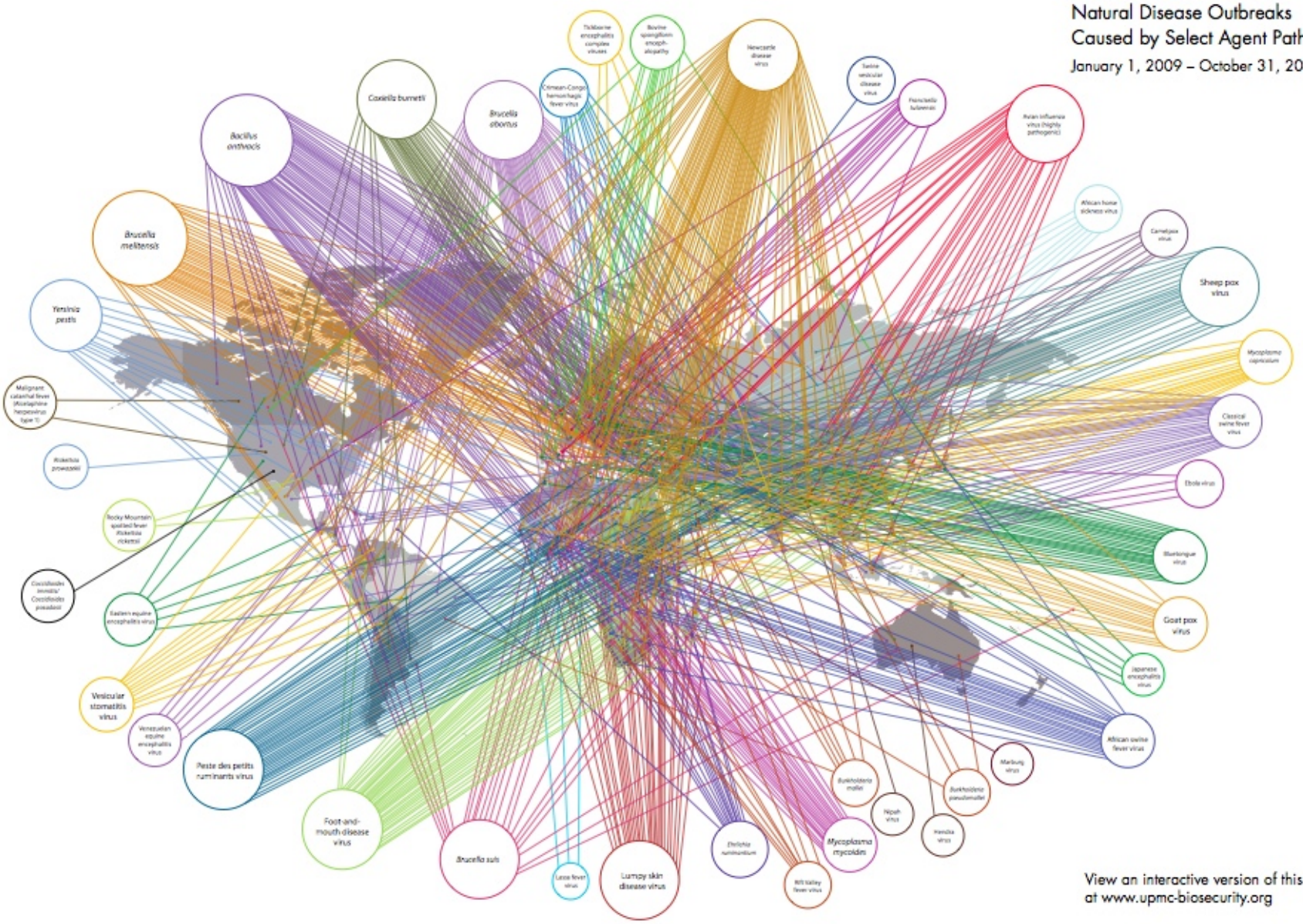
# Subsequent U.S. Government Policy Development

White House (OSTP and NSC) to lead interagency policy formulation process

Entire deliberative process record to be considered

- NSABB recommendation
- National Academies sessions
- Gryphon risk/benefit analysis
- Public comment (including comments on the final NSABB recommendation that NSABB will continue to accept as a courtesy, even after it has formally reported)

- Resulting U.S. policy to supersede funding pause


Natural Disease Outbreaks
Caused by Select Agent Pathogens
January 1, 2009 – October 31, 2010
Bacillus anthracis
Coxiella burnetii
Brucella abortus
Brucella melitensis
Yersinia pestis
Rickettsia prowazekii
Rocky Mountain spotted fever Rickettsia rickettsii
Eastern equine encephalitis virus
Vesicular stomatitis virus
Venezuelan equine encephalitis virus
Peste des petits ruminants virus
Foot-and-mouth disease virus
Brucella suis
Lumpy skin disease virus
Rift Valley fever virus
Ehrlichia ruminantium
Mycoplasma mycoides
Nipah virus
Hendra virus
Burkholderia mallei
Burkholderia pseudomallei
Marburg virus
African swine fever virus
Japanese encephalitis virus
Goat pox virus
Bluetongue virus
Ebola virus
Classical swine fever virus
Mycoplasma capricolum
Sheep pox virus
Camelpox virus
African horse sickness virus
Avian influenza virus (highly pathogenic)
Francisella tularensis
Swine vesicular disease virus
Newcastle disease virus
Bovine spongiform encephalopathy
Tickborne encephalitis complex viruses
Crimean-Congo hemorrhagic fever virus
Lassa fever virus
View an interactive version of this map
at www.upmc-biosecurity.org

# Links and Resources

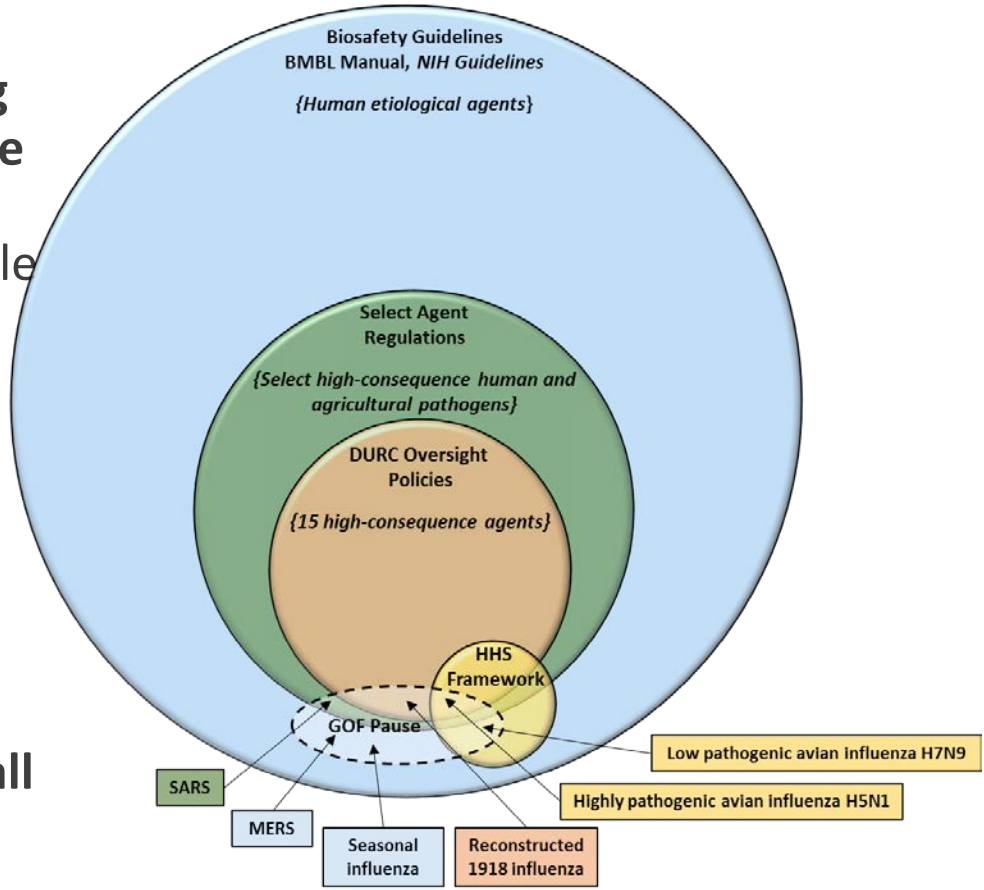
- **NSABB**
  - NSABB report, RBA, ethics paper, public comments, and more: http://osp.od.nih.gov/office-biotechnology-activities/biosecurity/nsabb
  - Past NSABB meeting materials and archived video casts: http://osp.od.nih.gov/office-biotechnology-activities/biosecurity/nsabb/nsabb-meetings-and-conferences/past-meetings
- **Gryphon Scientific**
  - RBA and supporting materials: http://www.gryphonscientific.com/gain-of-function/
- **National Academies**
  - First workshop summary (Dec. 2014): http://dels.nas.edu/Workshop-Summary/Potential-Risks-Benefits-Gain/21666?bname=bls
  - Second workshop summary (Mar. 2016): http://www.nap.edu/catalog/23484/gain-of-function-research-summary-of-the-second-symposium-march

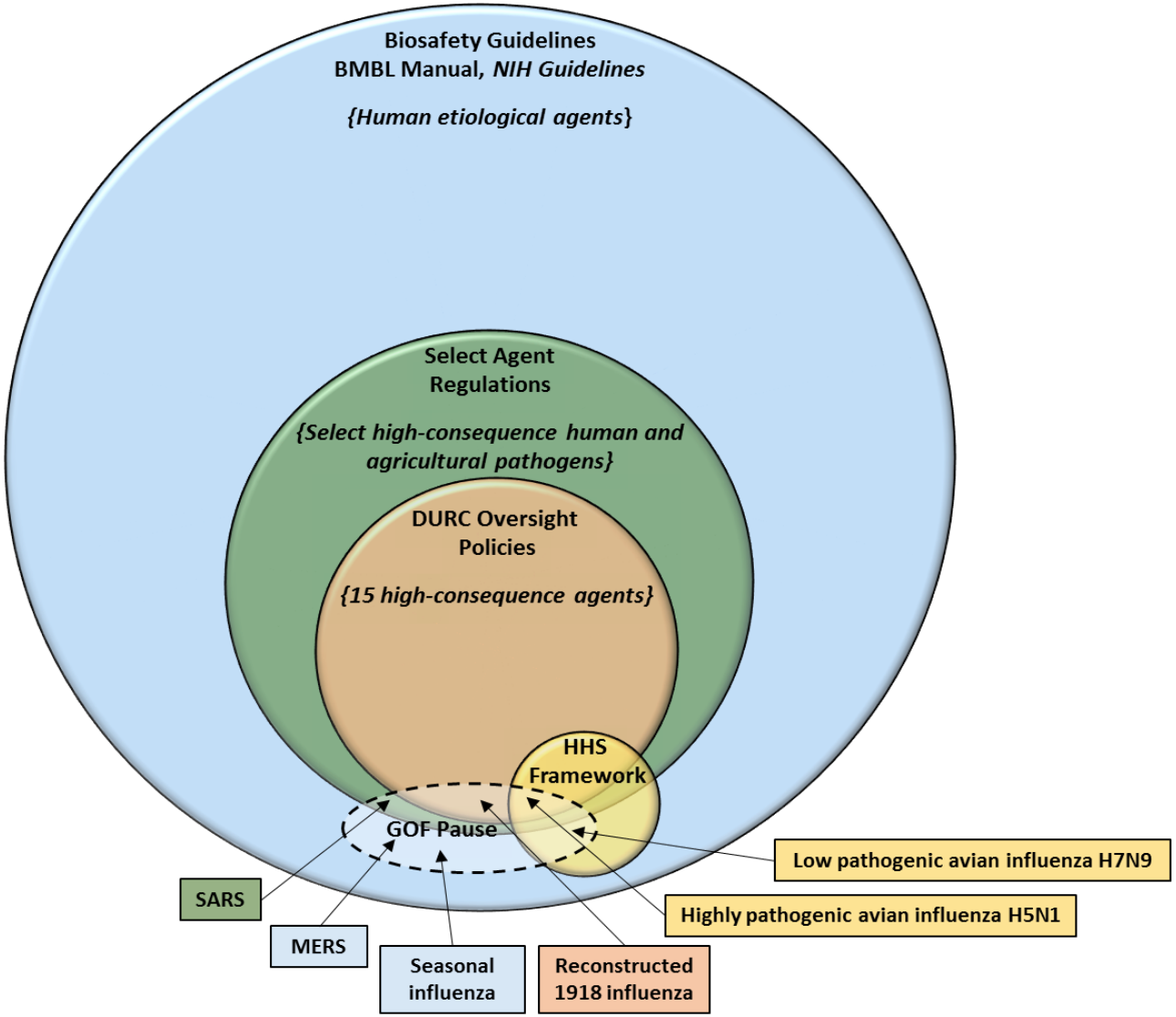
# *Thank you for your attention!*

# Findings of the NSABB WG

**<u>Finding 2.</u> The U.S. government has several policies in place for identifying and managing risks associated with life sciences research.** There are several points throughout the research life cycle where, if the policies are implemented effectively, risks can be managed and oversight of GOF research of concern could be implemented.

**<u>Finding 3.</u>** Oversight policies vary in scope and applicability, and do not cover all potential GOFROC, therefore, **current oversight is not sufficient for all GOF research of concern.**




Biosafety Guidelines
BMBL Manual, NIH Guidelines
{Human etiological agents}
Select Agent
Regulations
{Select high-consequence human and agricultural pathogens}
DURC Oversight
Policies
{15 high-consequence agents}
HHS
Framework
GOF Pause
SARS
MERS
Seasonal influenza
Reconstructed 1918 influenza
Highly pathogenic avian influenza H5N1
Low pathogenic avian influenza H7N9