

DURC Review at ISM-MS

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**Mount
Sinai**

DURC and the IBC

DURC reviews began in 2012 as a sub-group of the ISM-MS IBC, which:

- Looked at all research involving the **15-specified agents**
- Looked at the possible **7 DURC outcomes**:
 1. **Increase virulence**(Enhances the harmful consequences of the agent or toxin)
 2. **Overcomes immunity**(Disrupts immunity or the effectiveness of an immunization against the agent or toxin without clinical or agricultural justification)
 3. **Develop resistance to drugs. Avoid diagnosis.**(Confers to the agent or toxin resistance to clinically or agriculturally useful prophylactic or therapeutic interventions against that agent or toxin or facilitates their ability to evade detection methodologies)
 4. **Increase transmission**(Increases the stability, transmissibility, or the ability to disseminate the agent or toxin)
 5. **Change tropism**(Alters the host range or tropism of the agent or toxin)
 6. **Increase host susceptibility**(Enhances the susceptibility of a host population to the agent or toxin)
 7. **Regenerate extinct pathogens**(Generates or reconstitutes an eradicated or extinct agent or toxin listed above)

The ISM-MS DURC Questionnaire

PI:

Project Title:

Questionnaire

1. Does your research involve any of these 15 agents of special DURC interest?

- Yes (specify the agent)** **No**

If yes, give a brief description of the project and move to 2.

2. Does the research you are conducting with any of these 15 agents fall under one of the seven DURC categories?

- Yes (specify the category) _____** **No If no, briefly explain why this is the case**

If yes, move to 3. [Next Slide]

The ISM-MS DURC Questionnaire

- 3. Explain the scientific rationale behind your proposed experiments**
- 4. Explain the benefits to conduct this research. Is the information to be gained important for the field?**
- 5. Identify the possible Dual Use Research Concerns associated with this research**
- 6. Explain why the question addressed by the proposed research cannot be conducted with a pathogen outside the 15 DURC agents**
- 7. Develop a DURC mitigation plan. What measures will be applied to mitigate the possible dual use of the products (agents, information).**

An Example...

PI: Dr. X YZEEE

Project: *Host specific functions of the H5N1 polymerase*

Questionnaire

1. Does your research involve any of these 15 agents of special DURC interest?

Yes (specify the agent): Influenza A/Vietnam/1203/04 (H5N1) HALo mutant virus

No

If yes, give a brief description of the project and move to 2.

An Example...

The Influenza A/Vietnam/1203/04 (H5N1) HALo mutant virus (hereafter referred to as A/VN/1203/HALo) is an attenuated H5N1 virus generated from wild-type Influenza A/Vietnam/1203/04 (H5N1) virus by reverse genetics, as has been described (Steel, J., et al. J Virol. 2009 Feb; 83(4):1742-53).

We have also utilized A/VN/1203/HALo virus containing additional attenuating mutations in NS1 (N-terminal deletion at 99 amino acids), or PB2 (K627E, which lowers the efficiency of virus infection in mammalian cells).

Thus, all of our work use viruses derived from A/Vietnam/1203/04 (H5N1) that contain additional attenuating mutations in HA, NS1, and/or PB2.

An Example...

2. Does the research you are conducting with any of these 15 agents falls under one of the seven DURC categories?

Yes (specify the category)

No

If no, briefly explain why this is the case:

The mutations introduced in the virus *decrease*, rather than increase, the virulence and transmission of the agent

An Example...

3. Explain the scientific rationale behind your proposed experiments

Experiments using attenuated highly pathogenic avian influenza (HPAI) viruses seek to understand the roles of viral proteins in the virus life cycle, and their interactions with avian and human proteins in the cell.

This is a critical research agenda to understand why HPAI viruses are capable of infecting, and replicating in humans and other mammals. The work is focused on the polymerase complex (PB1, PB2, PA, as well as NP), and the synthesis of viral RNA that can activate innate immune systems.

The attenuated A/VN/1203/HALo virus is sufficient to address these questions experimentally in cultured human and avian cells, as it contains an intact polymerase complex.

The ability of HPAI viruses to transmit between species, or the roles of the HPAI HA in transmission, are not studied in these experiments.

An Example...

4. Explain the benefits to conduct this research. Is the information to be gained important for the field?

It is important- **indeed critical**- to understand HPAI viral polymerase mutants and interactions with host factors, as these mutations and host factors control whether an HPAI virus can replicate in human cells (and thus infect human beings). H5N1 HPAI viruses require a mutation in PB2, such as E627K, to synthesize viral RNA efficiently in human cells.

However, the molecular mechanisms governing this adaptation to humans is still unclear.

Earlier experimental work has addressed this question using attenuated A/VN/1203/HALo virus and polymerase replicon assays that contain no virus at all, and uncovered host proteins critical to HPAI polymerase adaptation to human cells.

This work provides novel drug targets, and understanding of host-virus interactions that control species jumping between birds and mammals

An Example...

5. Identify the possible DURC concerns associated with this research

There are no direct DURC's associated with the research project.

All of the attenuated A/VN/1203/HALo viruses generated and used are of *lower pathogenicity*, and *lower virulence*, than wild type HPAI A/Vietnam/1203/04 (H5N1) virus.

These viruses are already adapted to mammals to some extent, as wild- type A/Vietnam/1203/04 (H5N1) virus was isolated from a fatal human case.

The research *will not change tropism* beyond that which nature has already changed, nor increase virulence, overcome immunity, increase resistance to drugs, increase transmission, increase host susceptibility, or regenerate extinct pathogens.

An Example...

6. Explain why the question addressed by the proposed research cannot be conducted with a pathogen outside the 15 DURC agents

Polymerase from A/Vietnam/1203/04 (H5N1) virus or a similar H5N1 HPAI virus **must be used in these experiments**, as lab-adapted H1N1 strains such as WSN or PR8, or pdm H1N1, or other seasonal influenza strains, **are divergent from H5N1 polymerases.**

Intact wild type HPAI is not necessary for these experiments in cultured avian or human cells; An attenuated strain, A/VN/1203/HALo virus, is used in all research at this stage.

An Example...

7. Develop a DURC mitigation plan. What measures will be applied to mitigate the possible dual use of the products (agents, information).

A DURC mitigation plan includes measures to prevent dual use of these research reagents or results that can lead to DU capability.

As the A/VN/1203/HALo viruses are attenuated, dual use is not a high risk.

However, all work with A/VN/1203/HALo virus is performed by professional laboratory staff including faculty, students, and fellows, and all stocks of virus are accounted in laboratory notebooks and kept in secure laboratories.

An Example...

7. Develop a DURC mitigation plan. What measures will be applied to mitigate the possible dual use of the products (agents, information).[Continued]

The information developed from these studies is not easily adapted for dual use (nefarious) purposes.

It would require advanced laboratory capacity in influenza virology, and considerable sponsored basic research, to turn even peripheral results of these virus-host interaction studies into malignant biological agents.

However, if it were deemed so by NSABB or another agency, *results would only be disseminated as allowed by security protocols*, or research would be published in classified journals or redacted appropriately.

Conclusion

This presentation shows an actual Risk Assessment conducted on a research protocol that was determined to be of Dual Use Research Concern.

The steps used in the assessment are the same process used to evaluate any / all DURC at ISM-MS.

A new Committee has been developed (IDUCC) which is entirely separate from the original Institutional Biosafety Committee, although it shares many of the same members of the former committee.

The IDUCC will follow the DURC Guidance as found in the Companion Guide:
<http://www.phe.gov/s3/dualuse/Documents/durc-companion-guide.pdf>

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