THE UNIVERSITY OF CHICAGO

UNIVERSITY RESEARCH ADMINISTRATION

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CAROL ZUICHES
Associate Vice President for Research Administration
And Director, University Research Administration

August 27, 2012

Carole A. Heilman, Ph.D.
Director, DMID
NIAID, NIH, DHHS
6610 Rockledge Drive
Room 4209, MSC 6603
Bethesda, MD 20892-6603

RE: University of Chicago DURC review and policy implementation for award RO1-AI69227 (PI Olaf Schneewind)

Dear Dr. Heilman,

The above referenced NIH/NIAID DMID supported award has been identified as conducting experiments involving *Dual Use Research of Concern* (DURC), as described in the United States Government DURC Policy for Oversight of Life Sciences. Briefly, RO1-AI69227 seeks to develop conjugate vaccines against *Bacillus anthracis*, linking poly-D-γ-glutamic acid capsule (PDGA) with *B. anthracis* protective antigen (PA) or other proteins. Immune responses to vaccines are examined in experimental animals for protection against anthrax challenge with wild-type or mutant *B. anthracis* strains; these may lack either capsule or secreted toxins (for example PA) or may produce aberrant capsule molecules.

To address research activities in the Life Sciences with possible DURC, The University of Chicago (UC) has implemented new policy and has established a DURC Task Force. DURC projects are being identified via the Institutional Biosafety Committee (IBC) review mechanism, which analyzes all UC sponsored life science research activities involving recombinant DNA and/or agents pathogenic to man, animals or plants. The primary goals of the UC IBC DURC Task Force are to identify research with potential DURC concerns, to mitigate possible risks associated with this work, and to supervise the research activities using a mechanism of periodic review of investigator progress. Additional goals are to minimize the risks related to the misuse of the knowledge that is gained through UC DURC research on agents listed under US Government Policy for Oversight of Life Sciences DURC, Section III. This is being achieved by monitoring ongoing research activities of projects with identified DURC in 6 month intervals.

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With regard to the above referenced NIAID/DMID award, the UC IBC DURC Task Force has reviewed the *risk assessment statements* provided by Professor Schneewind (Attachment 1Ba) as stipulated in the recently published guidance documents from the NIH National Science Advisory Board for Biosecurity (NSABB), including *Responsible Communication of Life Sciences Research with Dual Use Potential*. The UC IBC DURC Task Force has reviewed the DURC risk analysis provided by Dr. Schneewind and provides the following recommendations:

1. **Design or conduct of the investigator's research with DURC.** Through his DURC risk analysis, Dr. Schneewind arrived at the conclusion that the work supported by this grant is dual-use research of concern. This determination is based upon the assumption that *Bacillus anthracis pagA* mutants are fully virulent in non-human primates and humans. Assuming this, the *B. anthracis pagA* mutants could pose a threat and be used as weapons against AVA immunized individuals, including military personnel already vaccinated, and those yet to be immunized with the stockpiled AVA vaccine. As such, the *pagA* mutant strains pose an immediate threat to vaccinated and unvaccinated individuals, as alternative vaccines are not yet available. The UC DURC Task Force believe that this immediate threat is mitigated by the fact that the *B. anthracis pagA* mutants generated to date remain sensitive to FDA-approved antibiotics, including levofloxacin and ciprofloxacin. The UC DURC Task Force is also in agreement with Professor Schneewind's assessment that the benefits of this research far outweigh the risks in that the product of this research, conjugate poly-D- γ-glutamic acid (PDGA) -based vaccines, are being tested for their efficacy against both wild-type *B. anthracis* strains as well as mutant strains that lack either capsule or secreted toxin. The UC DURC Task Force also believes that the work remaining to be completed with the support of this grant, which is to confirm the efficacy of the conjugate PDGA vaccines in *in vivo* assays demonstrating protection against challenge from wild-type or mutant *B. anthracis* strains, poses no additional DURC issues.

2. **Requirements for enhanced biosafety or biosecurity measures for the investigator's research with DURC.** The work supported by R01-AI69227 is conducted by Professor Schneewind's research group as part of the University of Chicago Select Agent Program and is carried out in the University of Chicago Howard T. Ricketts Regional Biocontainment Laboratory, which is located on the Department of Energy campus of Argonne National Laboratory (ANL). Therefore, this research program enjoys the benefit of all security features of the Ricketts Lab itself but is further protected by the ANL Campus access control. As such, this research program meets or exceeds all biosafety and biosecurity requirements not only promulgated by the CDC via the Select Agent Program but also those required by ANL and the United States Department of Energy. All personnel associated with this research program have been trained on biosafety and biosecurity procedures required for this Select Agent facility as well as on methods and options for reporting activities or behaviors inconsistent with these established biosafety and biosecurity-related procedures. Furthermore, all personnel associated with this research program have signed the UC Select Agent Program Code of Conduct (Attachment 2). As stated above, the UC DURC Task Force has requested semi-annual progress reports for the research supported by this grant and will be conducting an on-going review of the research outcomes and products. Beyond this, the UC DURC Task Force does not believe additional biosafety or biosecurity measures are necessary for management if this research program.

3. **Evaluation of existing evidence of medical countermeasure (MCM) efficacy.** As stated above in #1, while the *pagA* strains derived from this research are capable of circumventing AVA-based immunity, these strains have retained their sensitivity to FDA-approved antibiotics of choice for this organism, namely levofloxacin and ciprofloxacin.

4. **Utilizing the educational tools of NSABB on biosecurity and Dual Use Research of Concern to educate and train the investigator and the scientific team involved in this research.** Using the materials available from the NIH NSABB web site, the UC DURC Task Force has assembled a DURC training module that has been included as part of the annual UC Select Agent training program. The slides from this training module are attached (Attachment 3).

As we have already stated, the University of Chicago, its faculty investigators, and IBC/DURC Task Force members perform or supervise research activities for the benefit of humankind. Investigators performing research on development of vaccines (or other MCMs) must provide compelling arguments how such research can be beneficial and how its inherent risks may be mitigated. The product of such thoughtful design, review and implementation of DURC policy is designed to be the development of MCMs providing broad, rigorous protection against microbial threats as outlined by government policy.

We hope that the assessments provided herein by Professor Schneewind and the UC DURC Task Force will assist the NIAID in their assessment of the risks and benefits of this research. Please do not hesitate to contact us with questions or recommendations regarding our efforts to identify, manage and mitigate DURC related risks posed by our Select Agent research program.

Sincerely yours,

Carol Zuiches
Associate Vice President for Research Administration
Director, University Research Administration
Institutional Biosafety Committee/DURC Task Force Member
The University of Chicago

Joseph Kanabrocki, PhD
Assistant Dean for Biosafety
Institutional Biosafety Committee/DURC Task Force Member
Pritzker School of Medicine, Biological Sciences Division
The University of Chicago

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Institute of Allergy
and Infectious Diseases
Bethesda, Maryland 20892

September 21, 2012

Dr. Carol Zuiches
Associate Vice President for Research Administration
Director, University Research Administration
6030 S. Ellis Avenue, Room 114
Chicago, IL 60637

RE: R01AI69227

Dear Dr. Zuiches:

Again, I thank you and Dr. Kanabrocki for your letter of August 27, 2012 regarding the grant entitled "Surface proteins of *Bacillus anthracis*," awarded by the National Institute of Allergy and Infectious Diseases (NIAID), a component of the National Institutes of Health (NIH), to the University of Chicago (PI Olaf Schneewind, M.D., Ph.D.). We appreciate the documentation you provided regarding your risk mitigation plan, and our internal review found it adequate. We would also like to remind you of the DURC term of award on the Revised Notice of Award, issued May 17, 2012, stating that you should share with the Program Official any resulting manuscripts within 3 business days of planned journal submission for review and comment.

I would again like to thank you and all those who have been involved in this review for your efforts.

Sincerely,

Carole A. Heilman
Director, Division of Microbiology
and Infectious Diseases

cc: Dr. Joseph Breen
Dr. Michael Kurilla

Dr. Dennis Dixon
Ms. Mary Kirker

University of Wisconsin-Madison DURC Risk Mitigation Plan

Grant Number: R01AI095274-01A1

Principal Investigator: Eric Johnson, Sc.D.

Project Title: Characterization of Botulinum Neurotoxin A Subtypes

Design of Research

The goal of this study is to examine and compare the biological properties of the five botulinum neurotoxin (BoNT) A subtypes and determine which structural features are responsible for specific functions of the toxin. The knowledge gained from this study and the technical systems developed for expression and manipulation of recombinant BoNTs will positively and significantly impact the botulinum toxin research field as well as the medical field by providing the basis for potentially improved and alternative BoNT based therapeutics, which could significantly increase BoNT treatment options and indications.

Enhanced Biosafety and Biosecurity Measures

Biocontainment. The facilities occupied by Dr. Johnson's laboratory were designed to meet biocontainment standards outlined in Biosafety in Microbiological and Biomedical Laboratories (5th edition [1]; BMBL5) and exceed the requirements of working with *Clostridium botulinum* and botulinum toxin.

BSL-2 suite includes the following:

- Negative air-pressure lab
- Ongoing biosecurity monitoring
- An emergency generator in case of a power failure

BSL-3 suite includes the following:

- Negative air-pressure laboratories with active room pressure control
- Double-door autoclaves
- HEPA-filtered supply and exhaust air
- Gas decontamination ports
- An emergency generator in case of a power failure
- Other physical containment measures in the facility that operate without power
- Ongoing biosecurity monitoring
- Visual stack lights and audible alarms for ventilation system
- Exemption b3 [redacted]

Personal Protective Equipment (PPE). An essential component of risk mitigation is PPE. Staff follow recommendations in BMBL5 and the NIH Guidelines for Research Involving Recombinant DNA Molecules

BSL-2 PPE:

- Lab coat
- Safety glasses
- Nitrile gloves

BSL-3 PPE:

- Wrap front disposable smock
- Safety glasses

- Shoe covers
- Nitrile gloves

When exiting either the BSL-2 or BSL-3 suite, PPE is removed in a particular order and hands are washed with soap and water.

Operational precautions. Standard Operating Procedures (SOPs) provide risk mitigation. All activities in the Johnson laboratories are described in detailed SOPs including emergency response plans.

Personnel. All personnel undergo Select Agent security risk assessment by the United States Criminal Justice Information Services Division of the Federal Bureau of Investigation (FBI). Once approved by the CDC, but prior to initiating in experiments, each researcher must complete rigorous biosafety training, Select Agent training and one-on-one training with an experienced scientist. Refresher training is scheduled on a regular basis and when there is an update to an SOP. All training is documented. Dr. Johnson participates in training sessions and emphasizes compliance to maintain safe operations and a responsible research environment. As of April 03, 2013, UW-Madison meets all new requirements for Suitability Assessment for Tier 1 agents under 42 CFR Part 73.

Occupational health plan. The laboratory occupational health plan operates in compliance with the University of Wisconsin-Madison Occupational Medicine Program. The exposure control plan requires reporting to Dr. Johnson and the Responsible Official (RO) of all symptoms associated with botulinum intoxication and any instance of a potential exposure. The RO will communicate with the Infectious Disease Physician and Public Health authorities to ensure the individual gets antitoxin in an extremely timely manner.

Program oversight. The research program, procedures, occupational health plan, documentation, security and facilities are reviewed annually by the University of Wisconsin-Madison RO and at regular intervals by the CDC as part of the University of Wisconsin-Madison Select Agent registration. All recombinant DNA protocols are approved by the University of Wisconsin-Madison's Institutional Biosafety Committee after risk assessments were conducted by the Office of Biological Safety. In addition, the University of Wisconsin-Madison Biosecurity Task Force regularly reviews the research program and ongoing activities of the laboratory. The task force has a diverse skill set and provides support in the areas of biosafety, communications, facilities, compliance, legal, facilities, compliance, security and health. Members of the Biosecurity Task Force are in frequent contact with the principal investigator and laboratory personnel to provide oversight and assure biosecurity.

Evaluation of medical countermeasures

The only medical intervention currently available is antitoxin provided by the CDC. The vaccination is no longer available to personnel working in laboratories.

Notification of funding agency

If additional DURC data is identified, Dr. Johnson will notify his NIH Program Officer. Additional modifications to the risk mitigation plan will be made is necessary. All communications will be vetted using the UW-Madison DURC process and also will be sent to Dr. Johnson's NIH Program Officer.

Determining the venue and mode of communication

To advance the scientific mission, it is important for research results to be shared via peer-reviewed publications. However, if the research is considered DURC, additional discussions are necessary before sharing the information. When publication of DURC is planned, Dr. Johnson, the RO, Alternate Responsible Official (ARO) and Director of Research Communications will

- evaluate the benefits of publishing the manuscript (significance in the field, etc.)
- consider the risk that publishing the results could pose a serious threat in a reasonable timeframe

- determine how best to explain the value of the work to the scientific community and general public

develop a description of the biosafety and biosecurity measures in place to be included in the manuscript (2)
seek advice from NIH and others regarding the risk of publishing the research
develop press conference and talking point tools to put the work in context and to minimize sensationalism

Dr. Johnson and collaborators on the project will adhere to responsible communications guidelines (3) in written (emails, letters, publications, etc) and spoken (scientific presentations, informal talks, lectures, interviews, and informal discussions) communications.

Dual Use Research of Concern (DURC) Risk Mitigation

DURC training. The University of Wisconsin-Madison is currently determining which existing DURC training will be provided to PIs and research staff. Mostly likely we will use existing training which is available through the Southeast Regional Center of Excellence for Emerging Infections and Biodefense.

DURC Institutional Review. Dr. Johnson discusses potential DURC experiments with the University of Wisconsin-Madison's RO and ARO before an experiment is initiated. The RO and ARO conduct a risk assessment and compare the experiment and potential results to the U.S. Government Policy for Institutional Oversight of Life Science Dual Use Research of Concern. If deemed necessary, extra risk mitigation measures are required such as BSL-3. The RO will seek the advice of the IBC or Biosecurity Task Force if additional insight is required. The RO and ARO will also review experimental results.

1. http://www.cdc.gov/biosafety/publications/bmbl5/BMBL.pdf
2. http://oba.od.nih.gov/rdna/nih_guidelines_oba.html
3. http://oba.od.nih.gov/biosecurity/pdf/Communication_Tools_20_Dual_Use_Potential.pdf

References

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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April 30, 2013

Dr. William S. Mellon
Associate Dean for Research Policy
Bascom Hall
University of Wisconsin-Madison
500 Lincoln Drive
Madison, WI 53706-1380

RE: 1 R01AI095274-01A1

Dear Dr. Mellon:

We appreciate the documentation you provided regarding the Institution-approved DURC risk mitigation plan for NIH grant 1 R01AI095274-01A1, "Characterization of Botulinum Neurotoxin A Subtypes." It is clear that you and the University of Wisconsin-Madison devoted a great deal of time and care to conducting a risk assessment of this work and ensuring that the risk mitigation measures are consistent with those described in the March 29, 2012 United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern.

Our internal review of your risk mitigation plan found it to be consistent with the policy requirements and we have included it in the official grant file. We would remind you of the necessity for Dr. Johnson, through collaboration with the CDC, to conduct specific countermeasure testing of A4 and any other new toxin subtypes, and request that the Program Officer be apprised of progress and results.

We appreciate your efforts to work with DMID as we jointly manage this important research.

Sincerely,

Carole Heilman, Ph.D.
Director, Division of Microbiology
and Infectious Diseases, NIAID

Cc: Dr. Eric Johnson
Ms. Mary Kirker
Dr. Ryan Ranallo
Dr. Fred Cassels

University of Wisconsin-Madison DURC Risk Mitigation Plan

Grant Number: R56AI069274

Principal Investigator: Yoshihiro Kawaoka, DVM, PhD

Project Title: Transmissibility of avian influenza viruses in mammals

Modifying the design or conduct of the research.

Our research seeks to understand the mutations and mechanisms that would allow highly pathogenic avian H5N1 influenza viruses to infect humans and transmit among them. We, therefore, test the transmissibility of wild-type, reassortant, and mutant H5N1 viruses via respiratory droplets among ferrets, a well-established transmission model for influenza virus. In essence, we place naïve ferrets in wireframe cages next to ferrets inoculated with H5N1 viruses. This experimental setting prevents direct contact between inoculated and naïve ferrets, but allows virus transmission via aerosols. The experiments are designed to identify mutant residues responsible for altered host specificity and transmissibility, but are not designed to enhance the pathogenicity of H5N1 viruses. This information is critical for basic research and the public health sector to monitor circulating and newly emerging H5N1 strains for their pandemic potential and to develop countermeasures to such viruses.

These experiments must be conducted in the context of wild-type H5N1 viruses so that the data generated are biologically meaningful. Substituting attenuated strains is not a scientifically sound approach.

Enhanced Biosafety and Biosecurity Measures

Biocontainment. The facilities at University of Wisconsin-Madison Influenza Research Institute (IRI) were designed to exceed biocontainment standards outlined in Biosafety in Microbiological and Biomedical Laboratories (5th edition [1]; **BMBL5**).

BSL-3-enhanced suites include the following:

- entry/exit through a shower change room
- effluent decontamination
- negative air-pressure laboratories
- double-door autoclaves
- HEPA-filtered exhaust air
- gas decontamination room

BSL-3-Agriculture suite features include all those listed for BSL-3 enhanced plus:

- HEPA-filtered supply and double-HEPA-filtered exhaust air
- double-gasketed watertight and airtight seals
- airtight dampers on all ductwork
- the structure is pressure-decay tested annually

Additional facility risk mitigation measures include the following:

- Exemption b3
- built-in redundancies including two air handlers, two compressors, two filters each place filters are needed, two effluent sterilization tanks and two power feeds to the building
- an emergency generator in case of a power failure
- other physical containment measures in the facility that operate without power
- ongoing biosecurity monitoring

Personal Protective Equipment (PPE). An essential component of risk mitigation is PPE. In all studies involving highly pathogenic influenza, staff follow recommendations in **BMBL5** and the NIH Guidelines for Research

Involving Recombinant DNA Molecules (2; amended 2-21-2013 [3]). Staff change from street clothes to surgical-type scrubs and don the following PPE before transiting into the containment suites:

- disposable coveralls
- dedicated footwear and shoe covers
- head covers
- powered air-purifying respirators
- double gloves
- disposable sleeve covers (for some procedures; *required for experiments with transmissible highly pathogenic avian influenza A (HPAI) viruses*)

When exiting the facility, PPE is sprayed thoroughly with 70% ethanol, then all disposables (shoe covers, gloves, disposable sleeves, head covers, PAPR hoods and overalls) are discarded as waste to be autoclaved. Personnel take five-minute showers each time they exit a BSL-3 suite.

Operational precautions. In addition to the facility and PPE-mediated risk mitigation practices, Standard Operating Procedures (SOPs) provide risk mitigation. All activities in the Kawaoka BSL-3 facilities are described in detailed SOPs including emergency response plans.

Personnel. All personnel undergo Select Agent security risk assessment by the United States Criminal Justice Information Services Division of the Federal Bureau of Investigation (FBI). Once approved by the CDC and APHIS, but prior to initiating in BSL-3-level experiments, each researcher must complete rigorous biosafety training, Select Agent training and one-on-one BSL-3 training with an experienced scientist. Refresher training is scheduled on a regular basis and when there is an update to an SOP. All training is documented. Dr. Kawaoka participates in training sessions and emphasizes compliance to maintain safe operations and a responsible research environment.

Occupational Health Plan. The laboratory occupational health plan operates in compliance with the University of Wisconsin-Madison Occupational Medicine Program. Annual immunization with the seasonal influenza vaccine is required for all personnel. Baseline serum samples will be collected from individuals engaged in experiments involving transmissible H5N1 viruses. When a licensed HPAI H5N1 vaccine becomes available, individuals will be directed to receive this vaccination. (note: recently, BARDA has arranged for H5N1 vaccine to become available through a GlaxoSmith Kline clinical trial of an adjuvanted A/Indonesia/5/2005 (H5N1) vaccine.)

The Occupational Health plan requires reporting to Dr. Kawaoka and the Responsible Official (RO) of all respiratory symptoms associated with fever by any individual that has worked in a containment laboratory with H5N1 viruses. The RO will communicate with the Infectious Disease Physician and Public Health authorities.

Program oversight. The research program, procedures, occupational health plan, documentation, security and facilities are reviewed annually by the University of Wisconsin-Madison Responsible Official and at regular intervals by the CDC and the Animal and Plant Health Inspection Service (APHIS) as part of the University of Wisconsin-Madison Select Agent Program. All recombinant DNA protocols are approved by the University of Wisconsin-Madison's Institutional Biosafety Committee after risk assessments were conducted by the Office of Biological Safety. In addition, the University of Wisconsin-Madison Biosecurity Task Force regularly reviews the research program and ongoing activities of the laboratory. The task force has a diverse skill set and provides support in the areas of biosafety, communications, facilities, compliance, legal, security and health. Members of the Biosecurity Task Force are in frequent contact with the principal investigator and laboratory personnel to provide oversight and assure biosecurity.

Evaluation of medical countermeasures

The key medical countermeasures available for influenza virus include antivirals (currently, the only licensed antivirals of clinical value are neuraminidase inhibitors oseltamivir and zanamivir) and influenza vaccines against seasonal and pandemic viruses.

Antivirals. The parent influenza viruses used in this project have been shown to be sensitive to oseltamivir, an approved antiviral therapeutic. No mutations known to confer resistance to oseltamivir will be made to the

neuraminidase gene, the target of oseltamivir activity. If there is reasonable cause to re-evaluate antiviral sensitivity (e.g., due to evidence of a significant genetic change introduced by mutation or passaging), viruses will be retested to ensure they remain sensitive to oseltamivir.

Vaccines. Influenza vaccines, when available, are effective medical countermeasures. A prototype H5N1 vaccine against A/Vietnam/1203/2004 (H5N1) virus was shown to be effective in protecting against laboratory and mutant strains of the homologous virus based on hemagglutination inhibition experiments with human sera from vaccinated individuals (4). Sera from humans receiving an adjuvanted H5N1 vaccine developed by GlaxoSmith Kline (soon to be available to staff) showed good serocoversion following two vaccinations (5); good cross-clade protection with similar vaccines was shown in ferret studies (6).

Notification of Funding Agency

If additional DURC data is identified, Dr. Kawaoka will notify his NIIH Program Officer. Additional modifications to the risk mitigation plan will be made as necessary. All manuscripts containing DURC will be sent to Dr. Kawaoka's NIH Program Officer.

Determining the venue and mode of communication

To advance the scientific mission, it is important for research results to be shared via peer-reviewed publications. However, if the research is considered DURC, additional discussions are necessary before sharing the information. When publication of DURC is planned, Dr. Kawaoka, the RO, Alternate Responsible Official (ARO) and Director of Research Communications will

- evaluate the benefits of publishing the manuscript (significance to the field, etc.)
- consider the risk that publishing the results could pose a serious threat in a reasonable timeframe
- determine how best to explain the value of the work to the scientific community and general public
- develop a description of the biosafety and biosecurity measures in place to be included in the manuscript (4)
- seek advice from NIH and others regarding the risk of publishing the research
- develop press conference and talking point to help put the work in context and to minimize sensationalism

Dr. Kawaoka and collaborators on the project will adhere to responsible communications guidelines (7) in written (emails, letters, publications, etc) and spoken (scientific presentations, informal talks, lectures, interviews, and informal discussions) communications.

Dual Use Research of Concern (DURC) Risk Mitigation

DURC Training. The University of Wisconsin-Madison is currently determining which existing DURC training will be provided to PIs and research staff. Mostly likely we will use existing training which is available through the Southeast Regional Center of Excellence for Emerging Infections and Biodefense.

DURC Institutional Review. Dr. Kawaoka discusses potential DURC experiments with the University of Wisconsin-Madison's RO and ARO before an experiment is initiated. The RO and ARO conduct a risk assessment and compare the experiment and potential results to the U.S. Government Policy for Institutional Oversight of Life Science Dual Use Research of Concern. If deemed necessary, extra risk mitigation measure are required such as BSL3-Ag instead of BSL-3-enhanced or only certain personnel may conduct the experiments. The RO will seek the advice of the IBC or Biosecurity Task Force if additional insight is required. The RO and ARO will also review experimental results.

References

1. http://www.cdc.gov/biosafety/publications/bmbl5/BMBL.pdf

2. http://oba.od.nih.gov/rdna/nih_guidelines_oba.html
3. oba.od.nih.gov/oba/rac/amendments/MTRD_Gdl_Amdmts.pdf

4. Imai, M., Watanabe, T., Hatta, M., Das, S.C., Ozawa, M., Shinya, K., Zhong, G., Hanson, A., Katsura, H., Watanabe, S. Li, C., Kawakami, E., Yamada, S., Kiso, M., Suzuki, Y., Maher, E.A., Neumann, G., Kawaoka, Y. (2012) Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets. Nature, 486:420-428.
5. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM297037.pdf.
6. Baras, B., Stittelaar, K.J., Simon, J.H., Thoolen, R.J., Mossman, S.P., Pistoor, F.H., van Amerongen, G., Wettendorff, M.A., Hanon, E. and Osterhaus, A.D. (2008) Cross-protection against lethal H5N1 challenge in ferrets with an adjuvanted pandemic influenza vaccine. *PLoS One*, 3, e1401.
7. http://oba.od.nih.gov/biosecurity/pdf/Communication_Tools%20_Dual_Use_Potential.pdf

DEPARTMENT OF HEALTH & HUMAN SERVICES

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April 8, 2013

Yoshihiro Kawaoka, DVM, Ph.D.
Professor
Influenza Research Institute
Department of Pathobiological Sciences
School of Veterinary Medicine
University of Wisconsin-Madison
575 Science Drive
Madison, WI 53711

RE: 2R56AI069274-06

Dear Dr. Kawaoka:

We appreciate the documentation you provided regarding the Institution-approved DURC risk mitigation plan and the BSL3 enhancement procedures in place in your laboratory for NIH grant 2R56AI069274-06, "Transmissibility of Avian Influenza Viruses in Mammals." It is clear that you and the University of Wisconsin-Madison devoted a great deal of time and care to conducting a risk assessment of this work and ensuring that the risk mitigation measures are consistent with those described in the March 29, 2012 United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern. NIAID subject matter experts have reviewed the Institution's DURC risk mitigation plan. We appreciate the documentation you provided and our internal review of your risk mitigation plan found it to be consistent with the policy requirements. The final package of information is being assembled for review by the Core HHS Review Group. We will continue to keep you informed as the process goes forward.

Sincerely,

Carole Heilman, Ph.D.
Director, Division of Microbiology
and Infectious Diseases, NIAID

Cc: Ms. Mary Kirker
Dr. Teresa Haugel

University of Wisconsin-Madison DURC Risk Mitigation Plan

Grant Number: R01AI080598

Principal Investigator: Yoshihiro Kawaoka, DVM, PhD

Project Title: Molecular Mechanisms for the High Pathogenicity of 1918 Influenza Virus

Modifying the design or conduct of the research.

The goal of this study is to understand the pandemic potential of avian influenza viruses of subtype H1N1 that exist in nature. To this end, we test the transmissibility of mutant viruses in ferret models. However, no experiments are designed to enhance pathogenicity of influenza viruses.

These experiments must be conducted in the context of wild-type H1N1 viruses so that the data generated are biologically meaningful. Substituting attenuated strains is not a scientifically sound approach.

Enhanced Biosafety and Biosecurity Measures

Biocontainment. The facilities at University of Wisconsin-Madison Influenza Research Institute (IRI) were designed to exceed biocontainment standards outlined in Biosafety in Microbiological and Biomedical Laboratories (5th edition [1]; BMBL5).

BSL-3-enhanced suites include the following:

- entry/exit through a shower change room
- effluent decontamination
- negative air-pressure laboratories
- double-door autoclaves
- HEPA-filtered exhaust air
- gas decontamination ports

BSL-3-Agriculture suite features include all those listed for BSL-3 enhanced plus:

- HEPA-filtered supply and double-HEPA-filtered exhaust air
- double-gasketed watertight and airtight seals
- airtight dampers on all ductwork
- the structure is pressure decay tested annually

Additional facility risk mitigation measures include the following:

- Exemption b3
- built-in redundancies including two air handlers, two compressors, two filters each place filters are needed, two effluent sterilization tanks and two power feeds to the building
- an emergency generator in case of a power failure
- other physical containment measures in the facility that operate without power □ ongoing biosecurity monitoring

Personal Protective Equipment (PPE). An essential component of risk mitigation is PPE. In all studies involving highly pathogenic influenza, staff follow recommendations in BMBL5 and the NIH Guidelines for Research Involving Recombinant DNA Molecules (2). Staff change from street clothes to surgical-type scrubs and don the following PPE before transiting into the containment suites:

- disposable coveralls
- dedicated footwear and shoe covers
- head covers

- powered air-purifying respirators
- double gloves

When exiting the facility, PPE is sprayed thoroughly with 70% ethanol, then all disposables (shoe covers, gloves, disposable sleeves, head covers, PAPR hoods and overalls) are discarded as waste to be autoclaved. Personnel take five-minute showers each time they exit a BSL-3 suite.

Operational precautions. In addition to the facility and PPE-mediated risk mitigation practices, Standard Operating Procedures (SOPs) provide risk mitigation. All activities in the Kawaoka BSL-3 facilities are described in detailed SOPs including emergency response plans.

Personnel. All personnel undergo Select Agent security risk assessment by the United States Criminal Justice Information Services Division of the Federal Bureau of Investigation (FBI). Once approved by the CDC and APHIS, but prior to initiating in BSL-3-level experiments, each researcher must complete rigorous biosafety training, Select Agent training and one-on-one BSL-3 training with an experienced scientist. Refresher training is scheduled on a regular basis and when there is an update to an SOP. All training is documented. Dr. Kawaoka participates in training sessions and emphasizes compliance to maintain safe operations and a responsible research environment.

Occupational health plan. The laboratory occupational health plan operates in compliance with the University of Wisconsin-Madison Occupational Medicine Program. Annual immunization with the seasonal influenza vaccine is required for all personnel.

The Occupational Health plan requires reporting to Dr. Kawaoka and the Responsible Official (RO) of all respiratory symptoms associated with fever by any individual that has worked in a containment laboratory with H1N1 viruses. The RO will communicate with the Infectious Disease Physicians and Public Health authorities.

Program oversight. The research program, procedures, occupational health plan, documentation, security and facilities are reviewed annually by the University of Wisconsin-Madison IBC and at regular intervals by the CDC and the Animal and Plant Health Inspection Service (APHIS) as part of the University of WisconsinMadison Select Agent Program. All recombinant DNA protocols are approved by the University of WisconsinMadison's Institutional Biosafety Committee after risk assessments were conducted by the Office of Biological Safety. In addition, the University of Wisconsin-Madison Biosecurity Task Force regularly reviews the research program and ongoing activities of the laboratory. The task force has a diverse skill set and provides support in the areas of biosafety, communications, facilities, compliance, legal, facilities, compliance, security and health. Members of the Biosecurity Task Force are in frequent contact with the principal investigator and laboratory personnel to provide oversight and assure biosecurity.

Evaluation of medical countermeasures

The key medical countermeasures available for influenza virus include antivirals (currently, the only licensed antivirals of clinical value are neuraminidase inhibitors oseltamivir and zanamivir) and influenza vaccines against seasonal and pandemic viruses.

Antivirals. The parental influenza viruses used in this project have been shown to be sensitive to oseltamivir, an approved antiviral therapeutic. No mutations known to confer resistance to oseltamivir will be made to the neuraminidase gene, the target of oseltamivir activity. If there is reasonable cause to re-evaluate antiviral sensitivity (e.g., due to evidence of a significant genetic change introduced by mutation or passaging), viruses will be retested to ensure they remain sensitive to oseltamivir.

Vaccines. Individuals are vaccinated with a seasonal trivalent influenza vaccine, which contains a 2009 H1N1 component. Although we detected little cross reactivity in hemagglutination inhibition assays between 2009 H1N1 virus and an H1N1 virus used in this study, immunity to the 2009 H1N1 viruses is likely to provide some protection as observed in the 2009 pandemic in individuals previously exposed to early 20th century human H1N1 viruses.

Notification of funding agency

If additional DURC data is identified, Dr. Kawaoka will notify his NIIH Program Officer. Additional modifications to the risk mitigation plan will be made as necessary. All manuscripts containing DURC will be sent to Dr. Kawaoka's NIH Program Officer.

Determining the venue and mode of communication

To advance the scientific mission, it is important for research results to be shared via peer-reviewed publications. However, if the research is considered DURC, additional discussions are necessary before sharing the information. When publication of DURC is planned, Dr. Kawaoka, the RO, Alternate Responsible Official (ARO) and Director of Research Communications will

- evaluate the benefits of publishing the manuscript (significance in the field, etc.)
- consider the risk that publishing the results could pose a serious threat in a reasonable timeframe
- determine how best to explain the value of the work to the scientific community and general public
- develop a description of the biosafety and biosecurity measures in place to be included in the manuscript (3)
- seek advice from NIH and others regarding the risk of publishing the research
- develop press conference and talking point tools to put the work in context and to minimize sensationalism

Dr. Kawaoka and collaborators on the project will adhere to responsible communications guidelines (4) in written (emails, letters, publications, etc) and spoken (scientific presentations, informal talks, lectures, interviews, and informal discussions) communications.

Dual Use Research of Concern (DURC) Risk Mitigation

DURC training. The University of Wisconsin-Madison is currently determining which existing DURC training will be provided to PIs and research staff. Mostly likely we will use existing training which is available through the Southeast Regional Center of Excellence for Emerging Infections and Biodefense.

DURC Institutional Review. Dr. Kawaoka discusses potential DURC experiments with the University of Wisconsin-Madison's RO and ARO before an experiment is initiated. The RO and ARO conduct a risk assessment and compare the experiment and potential results to the U.S. Government Policy for Institutional Oversight of Life Science Dual Use Research of Concern. If deemed necessary, extra risk mitigation measure are required such as BSL3-Ag instead of BSL3+ or only certain personnel may conduct the experiments. The RO will seek the advice of the IBC or Biosecurity Task Force if additional insight is required. The RO and ARO will also review experimental results.

References

1. http://www.cdc.gov/biosafety/publications/bmbl5/BMBL.pdf
2. http://oba.od.nih.gov/rdna/nih_guidelines_oba.html
3. Imai, M., Watanabe, T., Hatta, M., Das, S.C., Ozawa, M., Shinya, K., Zhong, G., Hanson, A., Katsura, H., Watanabe, S. Li, C., Kawakami, E., Yamada, S., Kiso, M., Suzuki, Y., Maher, E.A., Neumann, G., Kawaoka, Y. (2012) Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets. Nature, 486:420-428.
4. http://oba.od.nih.gov/biosecurity/pdf/Communication_Tools%20_Dual_Use_Potential.pdf

DEPARTMENT OF HEALTH & HUMAN SERVICES

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April 10, 2013

Yoshihiro Kawaoka, DVM, Ph.D.
Professor
Influenza Research Institute
Department of Pathobiological Sciences
School of Veterinary Medicine
University of Wisconsin-Madison
575 Science Drive
Madison, WI 53711

RE: 5R01AI080598-04

Dear Dr. Kawaoka:

We appreciate the documentation you provided regarding the Institution-approved DURC risk mitigation plan and the BSL3 enhancement procedures in place in your laboratory for NIH grant 5R01AI080598-04, "Molecular Mechanisms for the High Pathogenicity of 1918 Influenza Virus." It is clear that you and the University of Wisconsin-Madison devoted a great deal of time and care to conducting a risk assessment of this work and ensuring that the risk mitigation measures are consistent with those described in the March 29, 2012 United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern. NIAID subject matter experts have reviewed the Institution's DURC risk mitigation plan. We appreciate the documentation you provided and our internal review of your risk mitigation plan found it to be consistent with the policy requirements.

Please remember that the Institution must comply in full with all the terms and conditions placed on this grant. If you have any questions about how to proceed, please contact Dr. Teresa Hauguel at hauguelt@niaid.nih.gov or (301) 594-8508.

Sincerely,

Carole Heilman, Ph.D.
Director, Division of Microbiology
and Infectious Diseases, NIAID

Cc: Ms. Mary Kirker
Dr. Teresa Haugel

DURC Questionnaire
(List of agents and categories on last page)

PI: Ron A.M. Fouchier, Erasmus MC Rotterdam, The Netherlands

Title of project: Studies on airborne transmissible A/H5N1 virus

Grant: NIAID-NIH HHSN266200700010C

1. Does your research involve any of the 15 agents listed in the US Government Policy for Oversight of Life Sciences Dual Use Research of Concern?

- ■ Yes, highly pathogenic avian influenza (HPAI)
- ☐ No

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

We have previously used site-directed mutagenesis and serial passage in ferrets, to generate HPAI A/H5N1 viruses that were transmitted between ferrets via aerosols or respiratory droplets (Herfst et al., Science, 2012). Viruses that were transmitted were subsequently sequenced using Sanger and deepsequencing techniques. In the current project, we want to identify the minimal set of mutations that is needed to confer airborne transmission of A/H5N1 virus between ferrets and test the effect of these mutations in the context of heterologous H5N1 virus backbones. Viruses harboring mutations associated with airborne transmission will also be evaluated in further transmission experiments and pathogenesis and fitness studies in mammals and birds and studies to evaluate the efficacy of vaccines and antivirals.

2. Does the research with any of these 15 agents fall under one of the seven categories listed in the US Government Policy for Oversight of Life Sciences Dual Use Research of Concern?

- ■ Yes (increase transmissibility, change tropism)
- ☐ No

Note: Although the project described here falls under the seven categories, it should be emphasized that the risks and benefits of this research have already been weighed extensively. A WHO-assembled group of influenza virus experts and the majority of NSABB members have judged that it is important to conduct this work and to publish the results. In this specific project, viruses will not be modified beyond the mutations already described by Herfst et al. and Imai et al. As a consequence, the potential risk of this research compared to the published data is negligible, while the benefits of increased fundamental knowledge are large. Furthermore, the research described in our paper published in Science and the conditions under which it was

performed (including the risk mitigation measures), were approved by both the Dutch and the US government.

If no, briefly explain why this is the case, and move to 4

If yes, move to 3

3. Explain the scientific rationale behind your proposed experiments

Since 1997, avian influenza A/H5N1 viruses sporadically cross the species barrier and infect humans, sometimes with a very severe clinical outcome. It is unclear what exactly determines the ability of such viruses to infect mammals. With the generation of airborne A/H5N1, we have created a unique possibility to study what is needed for an avian influenza virus to become pandemic in humans. By studying the required genetic properties, and the related phenotypic properties, we can now finally address the fundamental question of how human pandemic influenza viruses can emerge.

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

The recently published papers on H5N1 transmission have shown that the pandemic threat of H5N1 viruses is real: H5N1 viruses can be transmitted between mammals and the acquired mutations can accumulate in a single host in nature. Therefore, the results of the project described here, could help to better assess the risks of the current A/H5N1 epizootics for human health and would increase our understanding of the contribution of particular mutations or reassortment events and the biological traits they represent towards a transmissible virus. In other words it may have major value for prediction, prevention and treatment of the next pandemic.

5. Identify the possible DUR concerns associated with this research

Although it is unclear if the ferret-to-ferret transmissible virus would also be transmissible between humans, and also without any further knowledge of the efficiency of this potential human-to-human transmission and the pathogenicity of this virus, the possible dual use of this research comes from the fact that this virus could be used by someone with bad intentions. However, as described above, the real benefits of the research by far outweigh the hypothetical risks that information about our viruses would be misused.

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

By applying our research to HPAI H5N1 viruses, we 1) address a generic research question of utmost importance to the field, and 2) address a topic with direct application to a current threat. There is no alternative influenza virus (or any other pathogen) that can be used at the same time for the advancement of science and to help reduce a concrete public health threat.

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

All experiments will be conducted within the enhanced animal biosafety level 3 (ABSL3+) facility of Erasmus MC that was completed in 2007. The ABSL3+ facility consists of a negative pressurized (-30Pa) laboratory in which all *in vivo* and *in vitro* experimental work is carried out in class 3 isolators or class 3 biosafety cabinets, which are also negative pressurized (< -200Pa). Air released from the class 3 units is filtered by High Efficiency Particulate Air (HEPA) filters and then leaves via an independent duct of the facility ventilation system, again via a HEPA filter. Only authorized personnel that have received the appropriate training can access the ABSL3+ facility. For animal handling in the facilities, personnel always work in pairs.

All facilities, procedures, training records, safety drills, inventory records, and logbooks, are subject to inspection and oversight by the institutional biosafety officers of Erasmus MC in close consultation with the facility management. The facilities, personnel, and procedures are further inspected by the US Centers for Disease Control and Prevention (CDC) every 3 years in agreement with the US select agent regulations for oversees laboratories and by the Dutch government (ILT inspection). The most recent CDC inspections took place in February 2011 and March 2012 at which time no shortcomings in biosafety and biosecurity measures were identified. The Dutch ILT inspection in August 2012 did not reveal any shortcomings in the ABSL3+ facility according to Dutch legislation.

Although the laboratory is considered 'clean' because all experiments are conducted in closed cabinets and isolators, special personal protective equipment, including laboratory suits, gloves and FFP3 facemasks, is used and all personnel are offered seasonal and prototype A/H5N1 influenza vaccines with informed consent. Additional immunizations with A/H5N1 vaccine were administered if seroconversion could not be demonstrated. Consent records are held by the Department of Virology at Erasmus MC.

All personnel are given basic training in laboratory safety under BSL2 conditions. Employees are trained for a further 3 months under standard BSL3 conditions, supervised by highly experienced personnel. Following initial BSL3 training and a period of independent work under BSL3 conditions, employees are trained for a further 3 months in the ABSL3+ facility, again under the constant supervision of highly experienced personnel with >8 years of research experience. These training programs consist of handson work under supervision, following theory components on facilities, procedures and safety drills. Upon completion of the supervised training period, the supervisors judge whether trainees fulfill all requirements for working independently in the facilities. Annual refreshment training sessions on biosafety and biosecurity are provided by the principal investigators, biosafety officers, and facility managers.

All equipment in the facilities is monitored electronically and both acoustic and telephone alarms are employed to ensure that workers do not enter the facilities if equipment is malfunctioning. All personnel have been instructed and trained how to act in case of incidents. All incidents are handled with consultation between a senior staff member of the Virology Department, a clinical microbiologist, the biosafety officers, and the facility management. Antiviral drugs (oseltamivir and zanamivir) are directly available. Erasmus MC has isolation hospital rooms (negative pressure rooms with interlocks) with trained nursing and medical staff to be used in case of serious incidents and to quarantine the infected individual to prevent further dissemination of the pathogen.

The facility and the information systems are secured by procedures recognized as appropriate by the institutional biosafety officers and facility management at Erasmus MC and Dutch and United States government inspectors. Detailed information can not be described in this document, as that would be in conflict with the principles of security.

15 AGENTS

1) Avian influenza virus (highly pathogenic)
2) *Bacillus anthracis*
3) Botulinum neurotoxin
4) *Burkholderia mallei*
5) *Burkholderia pseudomallei*
6) Ebola virus
7) Foot-and-mouth disease virus
8) *Francisella tularensis*
9) Marburg virus
10) Reconstructed 1918 Influenza virus
11) Rinderpest virus
12) Toxin-producing strains of *Clostridium botulinum*
13) Variola major virus
14) Variola minor virus
15) *Yersinia pestis*

7 Categories of Research

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)

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April 9, 2013

M.W.J.C. (Mieke) Jansen, Ph.D.
Biosafety Officer, Environmental Safety Officer
Responsible Official Select Agents
Erasmus MC
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RE: NIAID-NIH-HHSN266200700010C

Dear Dr. Jansen:

We appreciate the documentation you provided regarding the Institution-approved DURC risk mitigation plan and the BSL3 enhancement procedures in place at Erasmus MC in your laboratory for Dr. Ron Fouchier's project funded under NIH contract HHSN266200700010C, "Studies on airborne transmissible A/H5N1 virus." It is clear that you, Dr. Fouchier and the Erasmus MC devoted a great deal of time and care to conducting a risk assessment of this work and ensuring that the risk mitigation measures are consistent with those described in the March 29, 2012 United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern. NIAID subject matter experts have reviewed the Institution's DURC risk mitigation plan. We appreciate the documentation you provided and our internal review of your risk mitigation plan found it to be consistent with the policy requirements. The final package of information is being assembled for review by the Core HHS Review Group. We will continue to keep you informed as the process goes forward.

Sincerely,

Carole Heilman, Ph.D.
Director, Division of Microbiology
and Infectious Diseases, NIAID

Cc: Dr. Ron Fouchier
Mr. Michael Finn
Dr. Diane Post