SESSION VIII
Research Investigator Perspectives on Implementation of the Institutional DURC Policy

Balaji Manicassamy
Assistant Professor
Department of Microbiology
University of Chicago

Institutional Biosafety Committees

Hyde Park Campus IBC

- Requires registration of ALL rDNA research
- Requires registration of all research involving pathogens (human, animal, plant)
- Requires registration of all research involving biological toxins

Select Agent IBC

- All UC Select Agent research
- All research conducted at the Howard T. Ricketts Regional Biocontainment Laboratory

UC DURC Task Force

Dave Pitrak, M.D.
Professor and Chief, Infectious Diseases
Chair-Select Agent Institutional Biosafety Committee

Nick Dulin, Ph.D.
Associate Professor of Medicine
Chair-Institutional Biosafety Committee

Gopal Thinakaran, Ph.D.
Professor of Neurobiology
Former Chair-Institutional Biosafety Committee

Sean Crosson, Ph.D.
Professor of Biochemistry and Molecular Biology
DURC Principal Investigator

Balaji Manicassamy, Ph.D.
Assistant Professor of Microbiology
DURC Principal Investigator

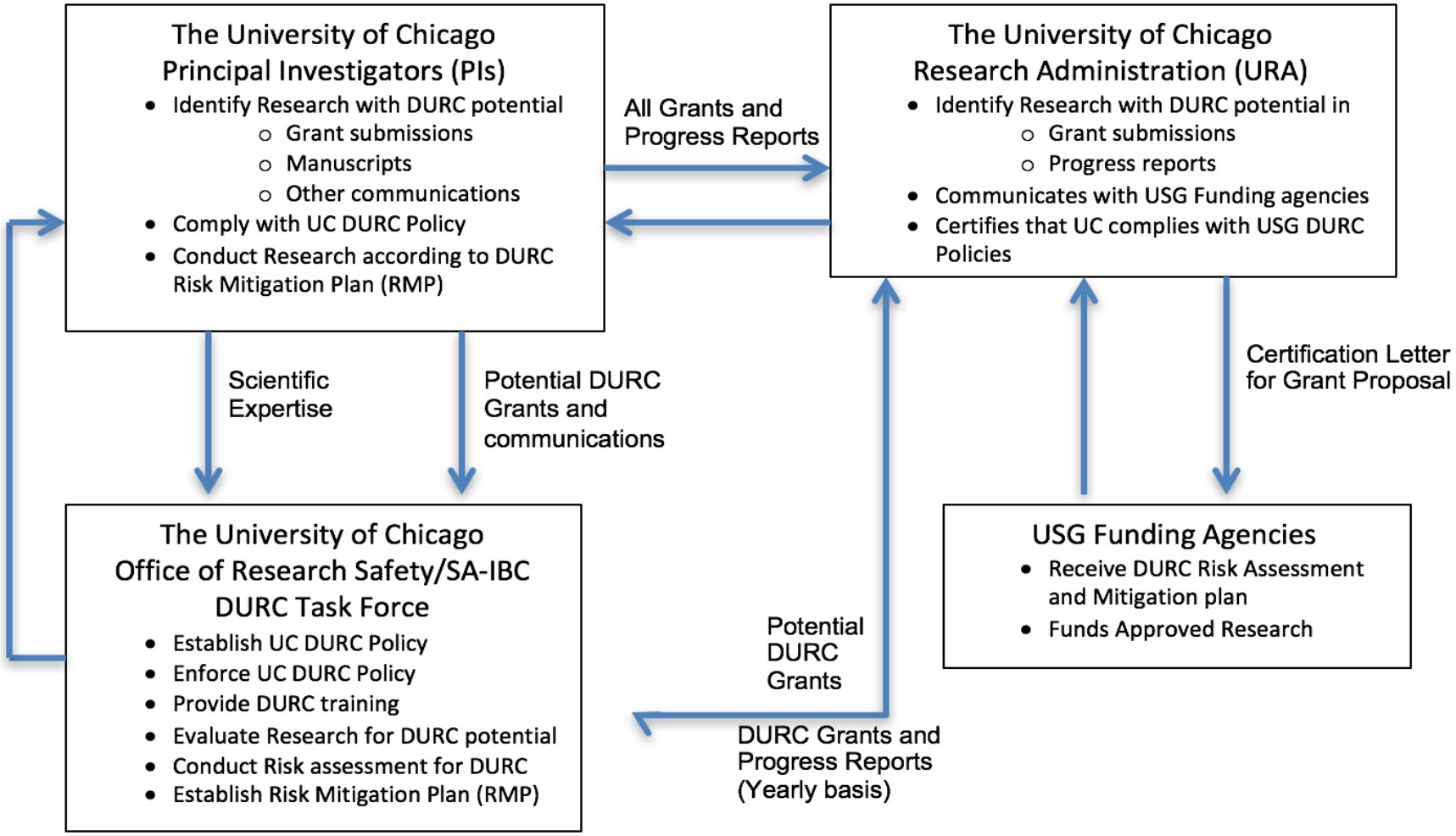
Mike Ludwig
Associate Vice-President and Director
University Research Administration

Russ Herron, J.D.
Senior Associate General Counsel
Office of General Counsel

Bill Pugh
Director
Office of Laboratory Regulatory Compliance

Joe Kanabrocki, Ph.D., NRCM(SM)
Professor of Microbiology
Associate Vice-President for Research Safety
Select Agent Responsible Official
Institutional Contact Dual-Use Research

DURC Governance



IBC and SA-IBC Protocol Submission

9.0 Dual-Use Research of Concern

Dual-Use Research of Concern (DURC) is defined as life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, material, or national security. An assessment of the proposed research for DURC potential is an essential element of the responsible and ethical conduct of research.

Assess your research plan for DURC by responding to the following questions concerning the potential experimental outcome:

Does the proposed research plan have the potential to alter the public health impact of the pathogen under study in one or more of the following ways:

1.0	* Enhances the harmful consequences of the agent or toxin.	○ Yes	● No Clear
2.0	* Disrupts immunity or the effectiveness of an immunization against the agent or toxin without clinical or agricultural justification.	○ Yes	● No Clear
3.0	* 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.	○ Yes	● No Clear
4.0	* Increases the stability, transmissibility, or the ability to disseminate the agent or toxin.	○ Yes	● No Clear
5.0	* Alters the host range or tropism of the agent or toxin.	○ Yes	● No Clear
6.0	* Enhances the susceptibility of a host population to the agent or toxin.	○ Yes	● No Clear
7.0	* Generates or reconstitutes an eradicated or extinct agent or toxin.	● Yes	○ No Clear
8.0	* Does this potential outcome have an immediate threat to public health and security?	○ Yes	● No Clear

If you answered "Yes" to one or more of the above types of experiments and "Yes" to question #8, you will be contacted by the Office of Biological Safety for assistance in developing a risk mitigation plan.

DURC Assessment and Communication

DFT assessment of DURC

1. **Could this research yield information that could be intentionally misused to threaten public health and safety or other aspects of national security?**
2. **What is the nature of the threat that could be posed from intentional misapplication of the information, and what are the potential consequences?**
3. **Could this research yield information that could potentially benefit the life sciences and/or public health and safety and other aspects of national security?**
4. **Do the potential risks of publishing these research findings and conducting the proposed experiments outweigh the potential benefits?**

USG Funding Agency – GOF Pause

- Oct 22, 2014 - K99/R00 grant flagged for GOF (2011-2015)
  - Mutations in NS1 gene (antagonist of host antiviral responses) PR8 strain
  - Previously reported mutations
- 90 day response time
- Preparation of response in discussions with Asst. BSO
- Assessment by UChicago DURC in Jan 16, 2015
- Approval of studies by NIH in Feb 22, 2015

Human Trials with PR8 (Risk Mitigation)

- Passaged in mice >300 times (Taylor RM, JEM 1941)
- Non-infective in humans due to HA and NA genes (H1N1)

TABLE II—COMPARISON OF THE LABORATORY AND VIRULENCE MARKERS OF Ao/PR8/34, A_2/ENGLAND/939/69, AND THE RECOMBINANT STRAINS (SEE MCCAHON AND SCHILD [10])

Virus	Growth in embryonated eggs	Virulence for mice	Growth at high temperatures	Virulence for man
Ao/PR8/34	++	++	++	Non-infective
A_2/Eng/939/69	±	−	±	++
PR8 × 939 (clone 6)	++	++	++	+
PR8 × 939 (clone 7)	++	−	++	++
PR8 × 939 (clone 64c)	+	++	++	Attenuated
PR8 × 939 (clone 64d)	+	−	±	Attenuated
X-31	++	++	++	Semi-attenuated

++ = high; ± = low; + = intermediate. The parents of X-31 [9] are thought to have been similar to those of the British recombinants.

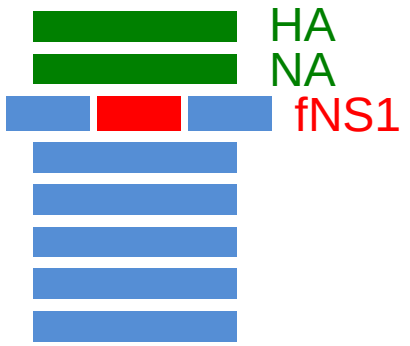
Beare and Hall, The Lancet 1971

USG Funding Agency – GOF Pause

- Feb 2, 2016 - R01 grant flagged for GOF studies prior to funding
  - Mutations in the NS1 gene of an avian H1N1 strain to allow interactions with human host factor
  - Risk mitigation using seasonal H1N1 HA/NA included in the proposal
- 15 day response deadline
- Preparation of response in discussions with Asst. BO
- Assessment by UChicago DURC taskforce submitted to NIH on Feb 19, 2016
- Approval of studies by NIH on March 29, 2016

Assessment and Recommendations by DURC Task Force at UChicago

- Aim 2b: Generate an avian virus with mutations in NS1 that allows interaction with a host factor (human)
- DK76 (H1N1 2009) + functional NS1
- **Risk Mitigation in the proposal:** Millions of individuals have protective antibodies against 2009 H1N1. Increase of NS1 function will not likely result in increase of virulence in humans.



- USG funding agency recommends to use PR8 HA/NA instead of 2009 H1N1 (HA/NA)
- Change in USG DURC policy to 15 agents
  - PO suggests that we could perform proposed studies

Lessons Learned

- Ongoing dialogues with BSO and review committee are important
  - Better understanding of the pathogen
- Assessment of DURC at institutional level has advantages
  - Face-to face meetings with BSO to develop risk mitigation plan
  - PI has opportunity to present risk and benefit analysis
- Changes in the mindset of students/staff
  - Potential risk assessment while designing the experiments
- Mostly design loss-of-function studies with BSL3 agents (H5N1, 1918)
- If necessary, perform gain-of-function studies in low pathogenic strains with risk mitigation steps
  - Vaccine and antivirals effective against this strain?
- Annual training of students/staff (BSL2 and BSL3 pathogens)
- Annual ethical code of conduct review by in person interview
- Reasonable time for DURC review and approval (~2-3 months)