BIORISK MANAGEMENT CASE STUDY: COLORADO STATE UNIVERSITY BIOSAFETY OFFICE

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SUMMARY

The Biosafety Office (BSO) is responsible for overseeing research biosafety and biosecurity at Colorado State University (CSU), which is a large public research institution in the United States. The CSU BSO is unique in that it oversees a wide range of research projects, including agricultural work and veterinary and large animal research, across a range of containment levels, including work at biosafety level (BSL)-3, animal biosafety level (ABSL)-3, and arthropod containment level (ACL)-3.

- The BSO emphasizes building positive relationships with researchers, embracing a spirit of collaboration over policing.

DISCLAIMER

Biosafety and biosecurity risk management practices can change over time. This case study represents one point in time and is a sample of an evolving set of risk management practices. For additional information on current practices please contact the organization directly.

CONTRIBUTORS

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THE VISIBILITY INITIATIVE FOR RESPONSIBLE SCIENCE (VIRS)

The goal of the Visibility Initiative for Responsible Science (VIRS) is to share information about the value of biorisk management and how life science stakeholder organizations approach the issue. VIRS was conceived by a multi-stakeholder group during an April 2019 working group meeting of the Biosecurity Innovation and Risk Reduction Initiative (BIRRI) program of NTI Global Biological Policy & Programs. With support from NTI, Stanford University Bio Policy & Leadership in Society VIRS produced a set of Case Studies in biorisk management, and The Biorisk Management Casebook that provides cross-cutting insights into contemporary practices.

THE BIORISK MANAGEMENT CASE STUDIES

The Biorisk Management Case Studies describes biorisk management processes for a diverse set of life science research stakeholders. The collection serves to evaluate the feasibility and value of knowledge sharing among both organizations that have similar roles and those that have different roles in managing research. Case studies were developed in consultation with organizations through a combination of research based on public sources, interviews, and providing a template with guiding questions for organizations to complete directly. Additional analysis can be found in The Biorisk Management Casebook: Insights into Contemporary Practices[1] in this collection. Project Directors: Megan Palmer, Stanford University; Sam Weiss Evans, Harvard University.

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ORGANIZATION BACKGROUND

Colorado State University (CSU) is a large public land-grant university in the United States and offers undergraduate and graduate degrees in the life sciences. The CSU Biosafety Office (BSO) "works with the Institutional Biosafety Committee (IBC) and the CSU research community to develop and implement appropriate biosafety practices, develop and conduct training programs, monitor and maintain compliance with regulations and guidelines, prevent/minimize personal, laboratory and environmental exposure to biological materials, conduct laboratory outreach visits, provide guidance on equipment and procedures, develop emergency plans for handling spills and personnel contamination, investigate laboratory incidents involving biological hazards, and report biosafety issues/noncompliance to appropriate CSU personnel and regulatory agencies."[2]

The BSO oversees an unusually large and complex range of life-science research activities for an academic institution. It operates across 3 campuses with facilities at biosafety level (BSL)-1, -2, and -3, animal biosafety level (ABSL)-1, -2, and -3, and arthropod containment level (ACL)-1, 2, and -3. These facilities conduct agricultural work, high-containment work, veterinary and large animal work, infectious disease research, wildlife disease research, field research, and vaccine manufacturing and are engaged in multiple external collaborations. They manage more than 50,000 square feet of high-containment research space used by a shifting set of researchers. The BSO interacts with life science researchers through in-person training, lab outreach visits, answering questions, and supporting institutional biosafety committee (IBC) review of projects before they start. Sometimes it also identifies projects that need review through more informal channels, such as conversations with researchers and staff.

While the BSO had previously been housed in an Environmental Health and Safety (EHS) department under the Vice President of Operations, a few years ago it was moved under the Vice President for Research as a stand-alone office. More recently, CSU biosafety activities were realigned in a newly created joint office under the leadership of the Biosafety Director. This move, which was suggested by external consultants, placed the BSO into the same structure as the IBC, Institutional Animal Care and Use Committee (IACUC), and Research Safety Culture Program to facilitate communication and coordination between these research compliance and oversight organizations. The current leadership at CSU has a strong biosafety and biosecurity background, including experience at U.S. government defense-related agencies, and was supportive of the restructuring.

The BSO also strives to develop and maintain positive relationships with researchers as a cornerstone of its approach. In its view, biosafety officers can sometimes be viewed by researchers as a kind of police force hindering research, rather than as a supporting and enabling factor for research. The BSO strives to deeply understand researchers' work, to treat them with respect, and to encourage proactive outreach and relationship building early in project development. The BSO believes this approach both improves safety and speeds up research.

PROCESS

Scope of risks considered

Given the diversity of research programs the BSO supports, it considers a wide range of biosafety and biosecurity risks. Many of the risks the BSO encounters regularly are related to laboratory biosafety, given its role as an organization that supports research within an academic institution. While some BSO staff tend to focus more narrowly on specific biosafety issues within laboratories, other staff members take a broader perspective to consider how research and institutional processes can help to foster a safe and secure research environment.

At a practical level, the BSO currently evaluates risks at the level of agents and projects, with each requiring an approval form (note that this process is in the process of being streamlined at the suggestion of external consultants):

- "An Agent Approval Request Form (AARF) is required for each infectious agent you have (or plan to have) in your possession; this applies to plant, animal, and human infectious agents." —CSU Office of Research Collaboration and Compliance[3] *(for an example form, see Appendix A[4])*
- "The Project Approval Request Form (PARF) is the form required for each submitted proposal that involves potential biosafety issues. It is indeed required for proposals that involve use of infectious agents (for which the AARF has been submitted previously or concurrently). It is also required for projects that utilize human body fluids or tissues, and for projects that involve use of recombinant DNA that is NOT exempt from review [according to National Institutes of Health Guidelines[5]]." —CSU Office of Research Collaboration and Compliance[3] *(for an example form, see Appendix B[6])*

The BSO strives to ensure that research that has been funded is conducted as safely and securely as possible; it does not consider broader ethical concerns (e.g., which research to fund) to be within its purview.

Overall sequence of steps

There is no one single series of steps the BSO uses to manage risks with life-science research projects at CSU. Broadly, its approach is based around entering into conversations with researchers about what they need to do their work and how they can do it at a mutually acceptable level of safety and security. They emphasize proactive and continual engagement, dialogue, flexibility, and shared goals and collaborative relationships with life scientists.

Projects can reach the BSO through a variety of avenues. Most commonly, projects will be flagged for additional review when researchers submit a research protocol to their IBC. Researchers, particularly those with more experience, will also reach out proactively to the BSO for advice on managing safety and security risks for particular projects. Other individuals who contact the BSO about specific projects include other researchers working in the same lab, grant administrators, greenhouse managers, animal care staff, occupational health, and university staff responsible for chemical safety. Keeping track of all the projects requiring BSO intervention can be challenging. The BSO has considered using automated systems, but it has been difficult to find the right system for a reasonable price; currently, the BSO tracks projects manually.

At a high level, risk management at the BSO involves gathering detailed information about a project, attempting to trace the causes of safety or security risks, and finding approaches to mitigate (not eliminate) risks as much as possible in ways that are workable for scientists and the BSO. If the BSO asks life scientists to change their work in a way that might impose burdens, they put effort into explaining why the changes are necessary for safety and they invite the scientists to help them think of other approaches. In their words, they "really try to exhaust the 'how do we make this work' line of thinking," which minimizes pushback from researchers. The BSO is also sensitive to life scientists' fears that their research would be shut down, even though this rarely occurs. As an example of this sensitivity, they avoid using the term "lab audit," and instead use "lab outreach visit."

BSO staff ultimately document their final decisions and justifications for approval, rejection, or modification in emails sent to researchers. These emails create a "paper trail" describing the outcome of the risk assessment that can be revisited later as needed.

Risk assessment

The BSO uses biosafety and biosecurity risk assessment forms to gather information about projects, including an Agent Approval Request Form[4] for work with infectious agents (whether animal, plant, or human) and a Project Approval Request Form[6] for projects that involve potential biosafety issues (see Appendices A and B). These forms were developed in concert with the IBC at CSU, and they ask for basic information about an agent or project that the IBC and BSO use to evaluate the project for biosafety and biosecurity concerns. Additional information may be collected through dialogue with the researcher(s) if needed, including in person, over the phone, or over email. All forms and procedures must be approved by the IBC and BSO before researchers are allowed to begin their work. The BSO also often identifies new risks during lab visits and in informal conversation with researchers, who in some cases may be directed to submit the appropriate forms for their work.

The BSO's risk assessments have been inspired in part by the Biorisk Assessment and Repository (BAR) tool developed by Barbara Owen and colleagues at Merck & Co., Inc., which consists of five sections: hazard identification, regulatory applicability, unit operation impact, risk mitigation and risk management strategy.[7] However, in keeping with the relationship-focused approach described above, the complete risk assessment and decision-making process is usually not formalized. BSO staff have a great deal of tacit knowledge they bring to bear on decisions on a case-by-case basis, and it is difficult to incorporate this knowledge into a standardized process. In addition, staff do not have time to conduct extensive formalized risk assessments for each life science project happening at CSU.

Assessing risks can be challenging even within the BSO, different team members have somewhat different risk tolerance levels, and these levels cannot be fully reconciled through a formalized process. Instead, BSO team members work together to find risk management solutions that are satisfying to everyone involved whenever possible. Ultimately, the Director of the BSO is responsible for the decisions made by the BSO and attempts to consider others' views and feedback to the extent possible.

Risk mitigation

The role of the BSO is to ensure research is conducted as safely and securely as possible; to that end, the BSO oversees the implementation of mitigation measures. In general, the BSO does not see prohibiting projects to be within its purview; instead, it views funding agencies as best equipped to decide what research should occur. However, the BSO can, in exceptional circumstances, prohibit researchers from working in high containment laboratories if it has concerns about their ability to conduct work safely and securely in that environment.

Researchers at CSU are required to fill out forms before beginning a life science research project, and these forms must be approved by the BSO and IBC before researchers are allowed to begin work in the lab. Part of this form includes a risk mitigation plan, including details like what personal protective equipment researchers will be wearing while conducting the research. If parts of the plan are viewed as insufficient by the BSO or IBC, they engage in additional conversations with the researchers to reach an understanding about the required mitigation measures.

Additional mitigation measures the BSO considers include:

- Requiring the use of specific decontamination procedures or disinfectants
- Requiring work be conducted in a specific facility or location
- Requiring researchers to have appropriate training
- Highly recommending that researchers receive certain vaccinations
- In the event of potential dual-use concerns, developing strategies to responsibly communicate research results
- Requiring additional physical security measures

Expertise required

Beyond qualifications and experience in biosafety, all BSO staff have previous experience as life science researchers, including work in fields such as microbiology, virology, veterinary medicine, wildlife biology, and radiology. According to the BSO, one key reason their approach to risk management is possible is the ability of BSO staff to understand the technical details of research and to empathize with the concerns of life scientists.

As noted above, risk assessment and mitigation at the CSU BSO relies on a great deal of both formal and tacit knowledge about biosecurity, biosafety, and the life sciences. This knowledge is often not written down and is transferred within the team through collaborative work, conversations, and "lunch and learn" sessions. Team members learn by doing, assessing and mitigating risks on a high volume of projects, as well as through external guidebooks and formal training. These include Biosafety in Microbiological and Biomedical Laboratories (BMBL),[8] which is an advisory document developed by the U.S. government, and courses provided by the American Biological Safety Association (ABSA).[9] The BSO encourages a culture in which staff are self-motivated to learn and ask for help, and to save and share reference information for particular topics to build a repository of team knowledge.

FEEDBACK

The BSO rarely receives feedback from researchers about whether their suggestions for improving biosafety or biosecurity have actually reduced the risk of biosafety and biosecurity incidents, because the base rates of these incidents are very low. However, it is sometimes able to notice more proximal measures of its success. For example, if a reporting system is not working as expected or life scientists are not filling out a form correctly, the BSO may realize it needs to adapt its approach. The BSO also receives social feedback from its life scientist collaborators. If BSO relationships with life scientists improve over time, it believes it is progressing toward biosafety and biosecurity.

SHARING

The CSU BSO shares information with colleagues at similarly situated organizations one-on-one upon request. CSU shares information through the networks it belongs to, including a network of U.S. laboratories engaged in biodefense or emerging infectious disease research (National Biocontainment Laboratories and Regional Biocontainment Laboratories[10]) and a separate community of U.S. government and academic research institutions focused on large-animal research (Research Alliance for Veterinary Science and Biodefense).[11]

REFLECTIONS

The BSO offers the following reflections about its experiences managing biosafety and biosecurity:

- In its interactions with researchers, the BSO emphasizes that it cares about the success of life science research at CSU. This allows the BSO to maintain a relatively high degree of rapport and open communication with researchers who might otherwise be wary.
- The BSO has benefitted from being open-minded about change, including periodically reviewing existing practices, policies, training, standard operating procedures (SOPs), and plans to see how well they are working. As part of this practice, the BSO routinely examines how it can more efficiently use researchers' time (while also gathering relevant information for the BSO and providing necessary training for the researchers) and how it can simplify existing practices so they are easier to understand and more useful for researchers.
- Dialogue with researchers is a core component of the BSO's risk management approach. While this can be useful for identifying risks and ensuring that they are managed appropriately, it can also be time-consuming for the BSO. To handle a large number of projects from across the university, the BSO affords its staff the independence to manage cases individually, with other staff members intervening only as needed.
- The BSO recommends putting in place institutional structures that enable groups with similar purviews to collaborate with one another. CSU recently brought together its IBC, IACUC (Institutional Animal Care and Use Committee), and Research Culture Office under the same umbrella, which has helped make research review more efficient.
- Third-party consultants can provide external validation for changes to institutional processes or structure, which may be helpful for getting critical support from an organization's leadership.

REFERENCES

1. Greene, D., Brink, K., Salm, M., Hoffmann, C., Evans, S. W., and Palmer, M. J. (2023). The Biorisk Management Casebook: Insights into Contemporary Practices. Stanford Digital Repository. Available at *https://purl.stanford.edu/hj505vf5601. https://doi.org/10.25740/hj505vf5601*.
2. CSU Biosafety Office. *https://www.research.colostate.edu/bso/*
3. Submit an Approval Request. *https://www.research.colostate.edu/ricro/ibc/forms/*
4. Example Agent Approval Form. *https://www.research.colostate.edu/ricro/wp-content/uploads/sites/22/2019/10/IBC_ExampleAARF.pdf*
5. NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules. *https://osp.od.nih.gov/biotechnology/nih-guidelines/*
6. Example Project Approval Form. *https://www.research.colostate.edu/ricro/wp-content/uploads/sites/22/2019/10/IBC_ExamplePARF.pdf*
7. Arizona Biosecurity Workshop, Dec. 7-8, 2017, Workshop Agenda. *https://www.asu.edu/ehs/biosafety/ASU-Biosecurity-Workshop-2017.pdf*
8. Biosafety in Microbiological and Biomedical Laboratories (BMBL) 6th Edition. *https://www.cdc.gov/labs/BMBL.html*
9. ABSA International. *https://absa.org/*
10. Biocontainment Research Facilities. *https://www.niaid.nih.gov/research/biocontainment-research-facilities*
11. Research Alliance for Veterinary Science and Biodefense BSL-3 Network (RAV3N). *https://rav3n.tamu.edu/*

APPENDIX A: EXAMPLE AGENT APPROVAL FORM

CSU RICRO Administator

View Agent Approval Form

Logout | Return to: Agent Approvals List | Main Menu

PI	[redacted]
Department	[redacted]
Investigator	(none)
Investigator	(none)
Investigator	(none)
Status	**Approved**
Date of original submission	2010-02-02
Date of initial approval	2010-02-10
Date of most recent approval	2010-02-10
Date of expiration	2011-02-10
Agent	**Adenovirus**
Strains	subtype 5 deletion mutant (Ad5dl309) and AdEasy vector
Human risk category	2
Vaccine available for people?	N
Vaccine used for personnel	N
Pathogenic for animals?	Y
Pathogenic for plants?	N
Antibiotic resistant?	N
CDC or USDA permit required?	N
Select agent?	N
Largest unconcentrated volume > 10 liters?	N
Will organism be radiolabeled	N
Planned release of the agent into the environment?	N
Methods of inactivation	Autoclave and chemical (Coverage plus viricidal)

Overview of how agent will be used

Normal morphological development of tissues during embryogenesis requires precise coordination of multiple cellular events such as cell migration and cell differentiation. Aberrant patterning of the nervous system results in severe congenital human diseases such as spina bifida. Prevention or treatment of these diseases requires an understanding of the machinery that controls neural patterning. The actin cytoskeleton is a fundamental cellular scaffold which dictates cell morphology and multiple important dynamic cell processes.

Cofilin is a member of a family of important actin assembly-regulatory proteins. Inactivation of cofilin-1 in mice results in neural tube closure defects, impaired neural crest migration and abnormal neuronal differentiation. The molecular and cellular basis of these developmental defects remains to be determined. We hypothesize that Wnt PCP signaling is coupled to cofilin regulation during vertebrate neural crest development. In this proposal we aim toidentify means by which Wnt signaling and cofilin govern neural crest patterning. We will use the chick as a model system to determine what Wnt activity controls neural crest migration in this vertebrate. Neural crest migration will be directly assessed in situ and in vitro by time lapse microscopy following specific inhibition of non canonical Wnt signaling through expression of dominant negative signaling intermediates or pharmacological inhibition. We will differentiate roles for canonical Wnt signaling versus non

canonical Wnt PCP and Wnt Calcium signaling pathways in neural crest patterning. We will identify Wnt ligands that stimulate neural crest migration and establish their cellular and molecular mechanisms.Cofilin activity in neural crest cells will be evaluated in response to treatments that either disrupt or stimulate Wnt PCP signaling. The role of cofilin and Wnt signaling on neural crest cell migration will be evaluated through 4D fluorescence confocal microscopy live cell imaging. We will analyze migration in whole chick embryos and neural crest explant cultures.

In vitro uses

In vitro BSL 2

Buildings for in vitro use [redacted]

Rooms for in vitro use [redacted]

Procedures used to protect personnel from exposure to agent during in vitro studies

BL-2: [redacted] has been approved as a BL-2 facility for generating and working with the recombinant bacterial plasmids and adenovirus in cell culture. The room is so labeled. It contains appropriate biological safety cabinet, centrifuge for viral work only, incubators for growing the cells, appropriate waste disposal facilities, and lab coats, gloves and eye protection that are worn when any viral work is performed. Adenovirus will be used

only in tissue culture. All personnel receive appropriate training on potential hazards and the necessary precautions. Eating, drinking, and other activities, which place individuals at risk,are not allowed in any laboratories in the building, including the BL-2 labs. Gloves,protective eyewear, and lab coats will be worn. All pipetting is done using mechanical pipettors. Solid waste of all types will be autoclaved prior to disposal. Liquid wastes are treated with 3% Coverage Plus or bleach to inactivate the virus prior to sewage disposal.

Cell culture work is done in a certified biological safety cabinet (service and certification is done annually). As is currently done for all work with human cell lines, solid waste of all types is autoclaved prior to disposal. Liquid wastes are processed with 3% Coverage Plus or 10% bleach prior to sewage disposal. No sharp objects of any kind are allowed in the biological safety cabinet under normal working conditions to prevent contamination by

puncture wounds. In the event of an accidental spill, the area will be immediately decontaminated with Coverage Plus (3%). All contaminated materials will be autoclaved. Prior to autoclaving contaminated materials,they are kept in a leakproof container in autoclavable bags. Both the container and bags are

clearly labeled as containing biohazardous materials. Janitorial staff will be notified of any changes in container location or type to avoid any accidental removal of materials [redacted] is labelled as BL-2 with indication that adenovirus is an infectious agent. This room has controlled access and only authorized workers who have been informed of the biohazard use this room.

In vivo uses

None

Original IBC Review

The CSU Biosafety Committee has reviewed your agent application for:

- Adenovirus

- In vitro at BSL 2

This application was APPROVED AS SUBMITTED.

The IBC greatly appreciated the level of detail provided in this Approval Request and would like to save it as an example for future applicants.

If you have any questions regarding this approval please contact Christine Johnson at 491-8690 or Chrsitine.Johnson@Colostate.Edu.

Thank you,

Christy

APPENDIX B: EXAMPLE PROJECT APPROVAL FORM

CSU RICRO Administator

View Project Approval Form

Logout | Return to: Project Approvals List | Main Menu

PI	[redacted]
Department	[redacted]
Investigator	(none)
Investigator	(none)
Investigator	(none)
Protocol number	10-014B
Status	Approved
Date of original submission	2010-02-02
Date of initial approval	2010-02-10
Date of most recent approval	2010-02-10
Date of expiration	2011-02-10
Project title	**Role of Cofilin and Wnt Signaling in Neural Crest Development**
Type of project	Extamural funding
Sponsor	NIH
PASS number	[redacted]
Locations of work	[redacted]
Project utilizes Select Agent(s)	No

Overview of Project

Normal morphological development of tissues during embryogenesis requires precise coordination of multiple cellular events such as cell migration and cell differentiation. Aberrant patterning of the nervous system results in severe congenital human diseases such as spina bifida. Prevention or treatment of these diseases requires an understanding of the machinery that controls neural patterning. The actin cytoskeleton is a fundamental cellular scaffold which dictates cell morphology and multiple important dynamic cell processes.

Cofilin is a member of a family of important actin assembly-regulatory proteins. Inactivation of cofilin-1 in mice results in neural tube closure defects, impaired neural crest migration and abnormal neuronal differentiation. The molecular and cellular basis of these developmental defects remains to be determined. We hypothesize that Wnt PCP signaling is coupled to cofilin regulation during vertebrate neural crest development. In this proposal we aim toidentify means by which Wnt signaling and cofilin govern neural crest patterning. We will use the chick as a model system to determine what Wnt activity controls neural crest migration in this vertebrate. Neural crest migration will be directly assessed in situ and in vitro by time lapse microscopy following specific inhibition of non canonical Wnt signaling through expression of dominant negative signaling intermediates or pharmacological inhibition. We will differentiate roles for canonical Wnt signaling versus non

canonical Wnt PCP and Wnt Calcium signaling pathways in neural crest patterning. We will identify Wnt ligands that stimulate neural crest migration and establish their cellular and molecular mechanisms.Cofilin activity in neural crest cells will be evaluated in response to treatments that either disrupt or stimulate Wnt PCP signaling. The role of cofilin and Wnt signaling on neural crest cell migration will be evaluated through 4D fluorescence confocal microscopy live cell imaging. We will analyze migration in whole chick embryos and neural crest explant cultures.

Infectious Agents

Name of Agent	Strains	Used in vitro?	Used in vivo?
Adenovirus	Ad5dl309	Yes at BSL 2	No

Dual use potential: No

Human-origin material

None

Toxins

None

Non-exempt recombinant DNA

cDNAs encoding various vertebrate proteins will be cloned into the AdEasy adenoviral expression system. We will use adenoviral mediated gene transfer to express the different cDNAs in cultured chick embryonic tissues.

- Source(s) of DNA to be expressed: from invertebrates and vertebrate animals including human
- Vector(s) used for delivery: Adenovirus
- Host(s) for expression of rDNA: cultured cells, chick embryonic tissue
- Proteins expressed via rDNA technology: cofilin, LIMK, slingshot, actin, RhoGTPases, PAKs
- NIH Guidelines category of non-exempt rDNA study: III-D-3
- Is the expressed product toxic to vertebrates: YES
- Is a federal permit required for this work: NO
- Is this a gene therapy trial: NO
- Are transgenic animals being generated: NO
- Are transgenic plants being generated: NO

Original IBC Review

The CSU Biosafety Committee has reviewed your project application for: Role of Cofilin and Wnt Signaling in Neural Crest Development (Project 10-014B).

This application was APPROVED AS SUBMITTED.

The IBC greatly appreciated the level of detail provided in this approval request and would like to save it as an example for future applicants.

If you have any questions regarding this approval please contact Christine Johnson at 491-8690 or Chrsitine.Johnson@Colostate.Edu.

Thank you,

Christy