Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format. Questions? Contact Health Research Program staff at 717-783-2548.

1. **Grantee Institution:** The Pennsylvania State University

2. **Reporting Period (start and end date of grant award period):** 1/1/2009 – 12/31/2012

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** John Anthony, MPA.

4. **Grant Contact Person's Telephone Number:** 814-935-1081

5. **Grant SAP Number:** # 4100047645

6. **Project Number and Title of Research Project:** Project 6 - *Research Infrastructure - Biological Research Laboratory Construction*

7. **Start and End Date of Research Project:** 1/1/2009 – 12/31/2012

8. **Name of Principal Investigator for the Research Project:** Mary J. Kennett, DVM, PhD, Diplomate ACLAM

9. **Research Project Expenses**.

   9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

   $ 311,524

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name	Position Title	% of Effort on Project	Cost
None			

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name	Position Title	% of Effort on Project
Mary Kennett	PI	< 1%

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
Individually ventilated animal cage (IVC) systems	Safe, sanitary cages	$216,425

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes___X_____ No_____

If yes, please indicate the source and amount of other funds:

Penn State funds (approximately $7,000,000)
NIH award - ARRA Penn State: ABSL-3 Facility Construction- $14,800,000

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes_____ No_____X_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If

you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
None	☐ NIH ☐Other federal (specify:_____) ☐ Nonfederal source (specify:_)			

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes____X_____ No_____

If yes, please describe your plans:

Once the laboratory is completed many investigators will apply for NIH or other funding for their research. Please see the answers to questions 12 and 15 for details on specific research areas and investigators who plan on using the facility.

12. Future of Research Project. What are the future plans for this research project?

The Biological Research Laboratory, an Animal Biosafety Level 3 (ABSL-3) facility, will be used for infectious disease research and will greatly enhance the research capabilities on campus. It is not possible to do research with highly infectious agents such as nza without proper protection and biocontainment. This facility will provide special air anthrax and avian influehandling capabilities to filter the exhausted air, liquid and solid waste decontamination, high security, and standard operating procedures within the facility to ensure the safe handling of such agents. The facility is organized into a central spine that connects all of the research spaces to the central decontamination and support areas of the project.

Members of the Penn State faculty are engaged in a continuum of theoretical, empirical, basic and translational research in infectious diseases. However, while we currently undertake data modeling on these agents, any experimental research must be done off campus. The proposed ABSL-3 facility will allow for advancement in all areas of our

research portfolio and provide a key facility in the geographical center of Pennsylvania. The four major areas of research excellence that will be enhanced by the ABSL-3 facility are discussed below:

1. Integrative studies on the theory, mechanism, and prevention of emerging and zoonotic infectious agents. Penn State has an internationally recognized and well-funded group of investigators (Drs. Cameron, He, Jayarao, Kapur, Lu, Poss, Cui, Holmes, etc.) conducting studies on emerging and zoonotic pathogens. While much of the extant research focuses on BSL-2 agents, the few examples of studies on BSL-3 agents currently being led by Penn State faculty include very virulent Newcastle Disease virus, the H5N1 Avian Influenza virus, and Hendra / Nipah virus (ABSL-4 agent). Needless to say, the work requiring high containment is all being conducted at facilities elsewhere. Led through the Huck Institute supported centers, including investigators in the Center for Infectious Disease Dynamics (www.cidd.psu.edu) and Center for Molecular Immunology and Infectious Disease (www.cmidd.psu.edu), the proposed ABSL-3 facility will enable a very large cadre of scientists to collaboratively conduct state-of-the art research that includes the evolution, ecology, and pathobiology of major BSL-2 and 3 emerging and zoonotic pathogens including Bunyaviruses, Paramyxoviruses, Retroviruses, Caliciviruses, *Francisella*, *Coxiella* etc. Our iterative use of theory, models, and empirical studies will integrate available knowledge of related BSL-2 agents and allow for focused, hypothesis driven research on BSL-3 agents in the new facility.

2. Vector-borne diseases**.** A number of Penn State faculty members (Drs. Hudson, Read, Thomas, Cui, Bjornstad, etc.) focus on how climate and anthropogenic changes in the environment influence the incidence, host-range, and disease dynamics of major insect vector borne diseases including Arboviruses such as West Nile virus, Rift Valley Fever, Dengue virus, and Blue tongue virus. For example a recent study undertaken by Dr. Peter Hudson's group has shown the vector borne pathogens are poorly served compared with their potential threat and a greater understanding will only emerge with detailed experimentations (in submission, *Science*). In particular we need to understand the dynamics of these infections to stop the spread of tick and mosquito borne infections in the USA. Expertise at Penn State in entomology, vector borne pathogens and the down scaling of climate models will provide some novel insights.

3. Study of pathogen - immune system interface using animal models**.** The study of innate / adaptive cellular immunity is well established at Penn State and will benefit considerably from the physical presence of the ABSL-3 facility. Research efforts to integrate molecular, cellular, and immunological studies with statistical and mathematical analysis and to synthesize the data across scales are ongoing, and evaluate pathogenesis and transmission in unique ways. This is critical because most infections, and many diseases, are not caused by a single pathogen. The complexity of polymicrobial infections requires new empirical and analytical solutions, many of which have already been established in ecology and evolutionary biology. The breadth of expertise actively being applied to these problems by the PSU infectious disease research community means that we are well suited to address these problems. Studies of immune system perturbations that occur when multiple infectious agents are present within a host are particularly important for translating research into therapeutics. This is an area in which there is considerable need, and also provides an

excellent opportunity to investigate within-host, pathogen-pathogen, or host-pathogen dynamics, research questions of intense interest among Penn State infectious disease investigators such as Drs. Kirimanjeswara, Schmitt, Rasgon, Marden, Dudley, DebRoy, Kariayawasam, Harvill and Kennett.

4. Vaccine development is an area of significant existing need and will be greatly enabled by the availability of the ABSL-3. Current activities of faculty at Penn State include: (i) the development of vaccine delivery platforms for various pathogens, (for instance, Dr. Biao He is currently supported for the development of vaccine delivery vectors for the H5N1 avian influenza virus with pandemic potential as well as very virulent Newcastle Disease Virus, etc.); (ii) Penn State faculty are either involved in or plan to work on the development of vaccines against bacterial agents (for example, Drs. Harvill and Kennett plan to work on vaccines for Bacillus anthracis and other respiratory pathogens); Dr. Vivek Kapur is currently involved in research on vaccine development for Yersinia pestis, Burkholderia spp., and Bacillus anthracis using iron-regulated outer membrane proteins); and, (iii) studies on the evolutionary and ecological impact and consequences of disease and control strategies, particularly studies on how pathogens evolve in response to vaccines (Hudson, Read, etc.). New investigators Drs. Sarkar and Kalia work on T cell memory in vaccine development.

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes_____ No_____x__

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male				
Female				
Unknown				
Total				

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic				
Unknown				
Total				

	Undergraduate	Masters	Pre-doc	Post-doc
White				
Black				
Asian				
Other				
Unknown				
Total				

14. Recruitment of Out-of–State Researchers. Did you bring researchers into Pennsylvania to carry out this research project?

Yes___X_____ No_____

If yes, please list the name and degree of each researcher and his/her previous affiliation:

We brought in a facility manager, John Henneman, B.A., M.S., RBP (Registered Biosafety Professional). His most recent position was manager of the BSL-3 facilities at Battelle in Ohio.

Girish Kirimanjeswara MVSc, PhD was hired as the Scientific Director for the facility. His most recent position was as a postdoctoral scholar at the ABSL-3 facility at Albany Medical College, NY.

15. Impact on Research Capacity and Quality. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes___X_____ No_____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

It has not been possible to perform BSL-3 research at PSU prior to the construction of this facility. This facility has excellent capacity due to the presence of an insectary, BSL-3, ABSL-3 and ABSL-3 enhanced suites. *The ABSL-3 facility is a key missing resource that will enable the development of a powerful multi-disciplinary infectious disease research pipeline at Penn State.* Infectious disease researchers at Penn State have made substantial advances due to the productivity of collaborative research teams that have formed around significant problems. We will harness the full potential of the ABSL-3 facilities by supporting these flexible, multidisciplinary research teams and provide them cutting-edge technology and resources. This will allow existing and newly recruited investigators to focus on important unanswered questions relating to infectious diseases and develop a translational pipeline for the development of the next generation of methods for prevention and surveillance. This is particularly important if we are to achieve the overall objective of substantially reducing the timeframe for translation of basic science research into clinically useful products and procedures.

Several Penn State investigators who are part of the Huck Institutes of the Life Sciences, the Center for Infectious Disease Dynamics, the Center for Molecular Immunology and Infectious Disease, and/or the Animal Diagnostic Laboratory are currently working with infectious diseases and are planning to extend their research program to the study of BSL-3 agents. Specifically, Dr. Kirimanjeswara will initiate research projects aimed at elucidating the pathogenesis of Tularemia caused by Tier I select agent *Francisella tularensis* using a mouse model. The planned research also focuses on determining the virulence factors that

make the bacterium highly fatal. He is currently funded by NIH and is conducting a part of the research at BSL-3 facility at Albany Medical College Albany, NY. Dr. Kirimanjeswara also plans to use the facility to understand the pathogenesis of Q fever caused by *Coxiella burnetii* and pneumonic plague caused by *Yersinia pestis*. Dr. Harvill will initiate the projects aimed at elucidating the host immune response following inhalation of *Burkholderia mallei* using a mouse model. Dr. Anthony Schmitt will study the mechanism of entry of Nipah virus into cells. He is currently using the BSL-3 facility U. of Maryland. Dr. Jason Rasgon will initiate projects focusing on the interaction of West Nile Virus with mosquitoes. He is currently carrying out part of the research at BSL-3 facility insectary at Wadsworth Center, Albany, NY. In addition, Dr. Bhushan Jayarao, the director of Animal Diagnostic Laboratory, a part of PADDL system of PA, will use the facility to carry out pathological and microbiological diagnostic assays. These Penn State PIs are currently limited by the lack of this facility and having to conduct the research at off-campus sites.

Dr. Lu uses poultry to develop rapid diagnostic tests for avian influenza. Dr. Cameron, a virologist, focuses on genomic replication of RNA viruses with the goal of antiviral drug development, while Dr. Holmes is interested in the adaptability of RNA viruses, viral fitness and viral emergence; these virologists would like to study Hepatitis C, SARS and Yellow Fever. Drs. DebRoy, Dunn, Kariyawasam, and Dudley currently study *E. coli* in poultry and mice and will extend their work to *Salmonella* sps and other zoonoses. Dr. Ottar Bjornstad is interested in the outbreak and persistence of infectious diseases with respect to population dynamics, competition, parasitism, and interactions between species. Drs. Poss and Hudson currently focus on the ecology of wildlife diseases, including zoonoses and plan to add additional agents of interest such as Hantavirus, West Nile Virus, and rickettsial diseases; they will use mice, rodents, ferrets, poultry and other domestic species for these studies. Drs. Read, Thomas and Cui currently study malaria and other vector borne pathogens in mice and rats, but will expand their work to include West Nile Virus, Rift Valley Fever, and potentially other vector borne BSL-3 diseases. Dr. Vivek Kapur's research focuses on the basic mechanisms of pathogenesis in two thematic areas: (i) microbial pathogenomics, including host response to infection; and, (ii) molecular epidemiology, including the study of population genetics of microbes. His BSL-3 work will cover pathogens such as *Yersinia pestis, Burkholderia sps., Mycobacterium* sps. and *Coxiella burnetii.*

Our specific objectives for the development and use of the ABSL-3 facility are to:

1. Organize a dynamic research consortium to support and facilitate investigator-directed basic, clinical and translational research on infectious agents and toxins;
2. Create a mechanism to provide support for critical technology and resource acquisition and upgrades;
3. Serve as a key resource for the development of a strong education and training program relating to infectious disease research.

Tobacco CURE funds were also used to purchase individually ventilated cage (IVC) systems. IVC systems are state of the art rodent housing systems. These systems utilize High Efficiency Particulate Air (HEPA) which is delivered to every cage in order to avoid stress, and ensure efficient ammonia and other waste gas removal. As a consequence the use of these caging systems create an improved, stable microenvironment that allows the expression

of natural and physiological behaviors in rodents. These caging systems also minimize the release of allergens into the room, thus protecting the investigators and animal care staff. In addition, IVCs reduce contamination and disease transfer among cages in the room due to the HEPA filters. Finally, IVCs help increase productivity and efficiency by reducing moisture in the cages thus allowing increased time between cage changes. These IVCs will benefit all biomedical research projects on campus that use mouse models. These caging systems provide the assurance of a suitable, stable, homogeneous environment for housing laboratory animals.

Tobacco funds were also recently used to purchase isolator units for housing germ-free and gnotobiotic animals. Isolators are required to house animals in a sterile environment in order to study the mechanisms by which microflora affect host systems. For example, intestinal bacteria are known to affect gastrointestinal homeostasis and the immune system via good barrier function and healing of injury. Several different mouse models will be housed in these isolators, and the microflora will be manipulated to help understand the role of various microorganisms and their interactions with the host in health and disease.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes_____ No_____X

If yes, please describe the collaborations:

16(B) Did the research project result in commercial development of any research products?

Yes_____ No__X___

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes_____ No____X_____

If yes, please describe involvement with community groups that resulted from the research project:

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). Indicate whether

or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

Initial scope of project

The scope of this project is to design and build an animal biosafety level three (ABSL-3) research laboratory for the study of immunology and infectious diseases requiring high level biocontainment**.** Even with the knowledge and biotechnology now available, we still face serious threats to human and animal health and well-being from serious and highly transmissible infectious diseases and / or potential agents of bioterrorism such as avian influenza and anthrax. To respond, we must create a research environment and provide the infrastructure necessary to allow investigators to study these pathogens and discover new ways to detect, prevent or cure these diseases. The proposed Biological Research Laboratory will provide space, support, and biocontainment for basic, applied and diagnostic research; national, state and community outreach; and education on important human and animal pathogens. It will include state-of-the-art laboratories and animal resources, facilities and services that are recognized within and outside the University as being of the very highest quality consistent with our talents and resources. This facility will be composed of a number of ABSL-3 suites for *in vivo* research using small animal models of disease (primarily rodents and poultry). Each suite will have

independent ante rooms to support multiple agent research as well as providing compartmentalization to mitigate cross-contamination concerns. Changing rooms and shower out facilities are included as required. Supporting the ABSL-3 suites will be BSL-3 laboratories for *in vitro* bacteriology, virology, and molecular biology procedures. Outside of the biocontainment area another support laboratory provides preparatory space for the activities within the barrier. The strategically located management office allows for oversight of the main entry way as well as the loading dock. A conference/classroom/break room allows for on-site training sessions and staff meetings. This $8,000,000 building project will encompass over 5,000 gross square feet, and will provide laboratories as well as animal holding space that will support the critical need for biocontainment research space at the Pennsylvania State University. This facility will be a unique and much needed resource for infectious disease research. In addition, support space (to house an IVIS imaging camera) and an adjacent biohazard animal holding room in Henning building will be renovated to support preliminary infectious disease studies. This imaging system has the flexibility to image fluorescent and/or bioluminescent reporters both in vivo and in vitro to facilitate non-invasive longitudinal monitoring of disease progression, cell trafficking and gene expression patterns in living animals.

Revised Scope and summary of Research Completed

A site was chosen and an initial design was developed. The preliminary plans were brought before the planning commission, township, and the community, and were well received. However, the project cost estimates were greater than the available budget. Fortunately, the NIH has issued an RFA (RFA-RR-09-008) entitled Recovery Act Limited Competition: Extramural research Facilities Improvement Program (CO6), which provides funding for the construction of facilities such as this. In accordance, we redesigned the facility to include additional features such as an insectary, a second BSL-3 laboratory and a second shower, as well as improved the redundancy of the building systems and submitted a proposal for an enhanced building project consisting of a 20,000 GSF animal biosafety level three (ABSL-3) facility. The new floor plan is shown in Figure 1, and will include microbiology and virology laboratories, cell sorting capabilities, animal biocontainment suites, and an insectary. This enhanced facility will support the study of emerging and zoonotic agents, vector borne diseases, the host pathogen interface, and vaccine development. We met with interested faculty groups to identify their biocontainment research needs, and designed the facility with respect to the identified and predicted need for each type of space with as much flexibility as possible within the constraints of BSL-3 design. The site for the building, near the current Animal Diagnostic Lab, was chosen as it is easily accessible from central campus and yet not near dense student populations.

The redesigned ABSL-3 facility proposal that was submitted as an NIH CO6 construction project includes state-of-the-art laboratories, animal housing and procedure room suites, and a BSL-3 insectary. Specifically, the building will contain two single ABSL-3 animal holding room (AHR)/procedure room suites (an animal holding room with an associated procedure room and ante-room), and two double AHR suites (two AHRs separated by a procedure room and ante-room/air-lock). One of the double AHR suites will have enhanced (ABSL-3E) filtration and air handling capacity and will be designed to hold poultry isolators for avian influenza studies. The other AHR suites will hold up to three biocontainment rodent racks per animal holding room. The building will also contain two BSL-3 laboratories for *in vitro* microbiology and virology

studies, as well as two small labs for flow cytometry, PCR and freezer storage. A small insectary will also be housed within the containment space for work with vector-borne agents. Completing the containment space are a feed and bedding storage space, a gas/decontamination chamber, an autoclave, and shower out facilities. Outside of containment, there will be a preparatory/support laboratory, a conference/ training/ break room, the manager's office, the loading dock with secure waste and cylinder storage, as well as the main entrance and restroom facilities. See Figure 1 for the floor plan and Table 1 for a list of room dimensions. The research space will be located on the ground floor with the HVAC and mechanical, electrical and plumbing (MEP) systems, including a liquid effluent decontamination system, on the floors above and below.

The building is designed to meet construction and redundancy standards as described in the NIH Design Policy and Guidelines for ABSL-3 and ABSL-3 enhanced research space for high pathogenicity infections (such as avian influenza). The building includes numerous security features including a perimeter fence, card or proximity reader access, biometric security to access the containment zone, as well as motion detectors, lights and security cameras. Several levels of security will be in place, only limited access to the facility will be allowed, and all entries will be documented. Training and security clearances will be required prior to entry according to a biosafety manual specific to the BRL. Standard Operating Procedures (SOPs) will be developed specifically for the BRL to train and certify all personnel working within containment, to ensure safety and security according to Occupational Health and Safety guidelines. Specific policies will be developed for practices such as showering, minimal sharps use, and decontamination. Procedures will be in place to minimize the production of aerosols, and all animal specific regulations and biosafety procedures will be followed. Biohazardous materials use authorization (Recombinant DNA or Human Pathogen registration, Select Agent use etc.) will be instituted as appropriate.

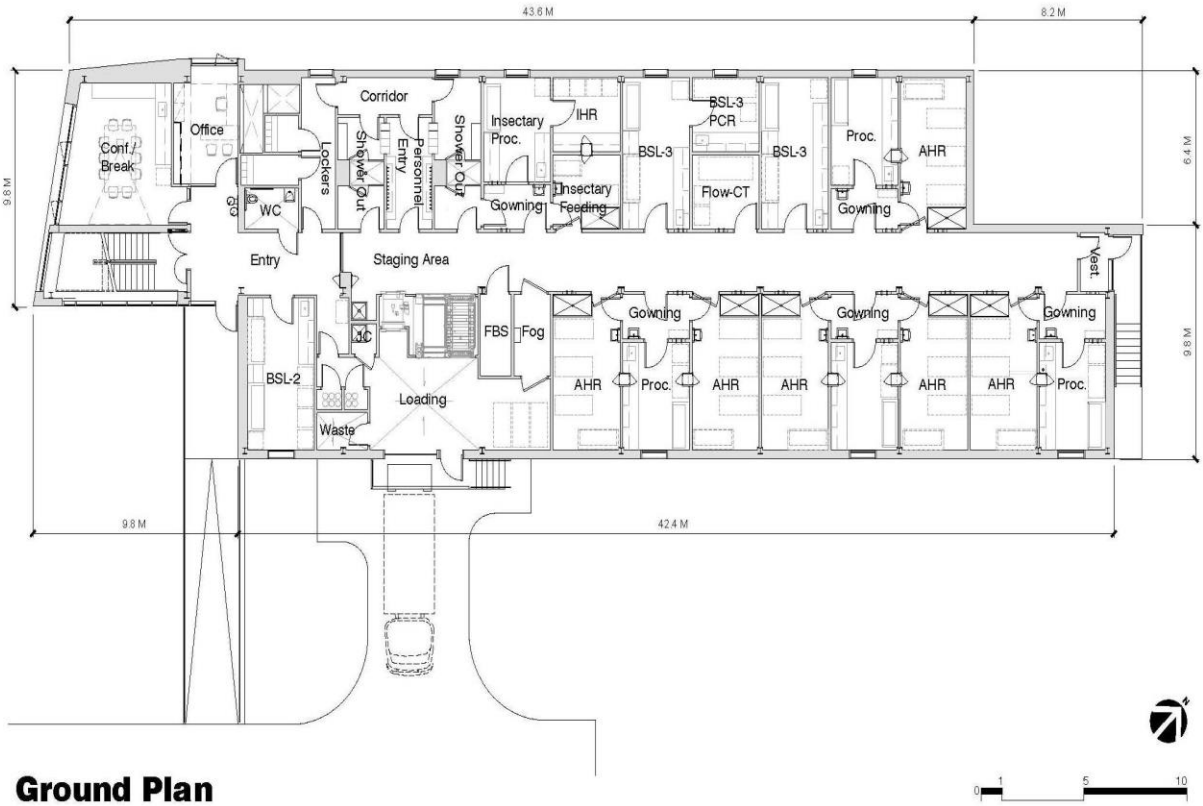

Figure 1. Floor plan for the BRL research space: Animal holding room (AHR), Insect holding room (IHR), Procedure room (Proc.), Feed and bedding storage (FBS), Gas decontamination chamber (Fog)

Table 1. List of room dimensions					
ROOM/ SPACE	**# of Units**	**NSM/ Unit**	**Total NSM**	**NSF/ Unit**	**Total NSF**
Non-Containment Space					
Entry	1	27	27	288	288
Conference/Break Room	1	30	30	322	322
Office	1	15	15	156	156
Locker Rooms	1	16	16	175	175
WC	1	5	5	48	48
Shower Out	1	12	12	124	124
Loading Dock	1	35	35	375	375
Waste Storage	1	4	4	41	41
Cylinder Storage	1	2	2	20	20
JC	1	1	1	14	14
BSL-2	1	20	20	218	218
Non-Containment Sub Total			**167**		**1,781**
BSL-3 Space					
BSL-3 Laboratory	2	20	40	218	436
BSL-3 PCR	1	10	10	106	106
Flow Cytometry	1	10	10	106	106
BSL-3 Sub Total			**60**		**648**
ABSL-3 Space					
Gowning Airlock	4	5	20	58	232
ABSL-3 Procedure	4	14	57	154	616
Animal Holding Rooms	6	20	120	217	1,302
Insectary Suite					
Gowning Airlock	1	6	6	64	64
Procedure	1	15	15	149	149
Animal Holding Room	1	10	10	109	109
Insect Holding Room	1	10	10	109	109
ABSL-3 Sub Total			**238**		**2,581**
In Containment Support Space					
Contained Corridor/Staging	1	97	97	1040	1,040
Fogging Chamber	1	6	6	63	63
Food & Bedding Storage	1	5	5	55	55
Shower Out	2	6	12	62	124
Support Sub Total			**119**		**1,282**
Subtotal Net Square Footage			**584**		**6,292**
Building Gross Square Footage			**1,858**		**20,000**

The NIH/National Center for Research Resources (NCRR) Recovery Act Construction Program proposal was successful and an award of $14.8 million was received in 2010 to expand the facility. In accordance with the guidelines of the award, a phase 1 archeological review was performed and an environmental assessment was completed. In addition, we have redesigned the facility to include additional features such as an insectary, a second BSL-3 laboratory and a second shower, as well as improved the redundancy of the building systems. The new containment zones are illustrated in Figure 2 and an artist's rendering of the BRL is shown in Figure 3. In June 2010 we received approval from the NIH to continue using Torcon, Inc. construction management (CM) services as Torcon provided constructability and cost estimating services during the design process. By October Torcon had prepared a preliminary Guaranteed Maximum Price (GMP) for use by Penn State officials. The Penn State Board of Trustees approved the preliminary GMP and granted approval for the project in November, and Penn State and Torcon begin preparing subcontractor packages and subcontractor requirements in December of 2010.

In 2011 the environmental assessment was completed and a signed Finding of No Significant Impact (FONSI) was issued. The design team completed final design documents and submitted them to the NIH technical review team. The NIH architects and engineers reviewed the project in detail and approved the construction documents. Bids were accepted in early 2011 and reviewed. The bid package for a CM at risk, including the final GMP as well as a discussion of the pre-qual, pre-bid, and bidding process, was submitted and NIH issued a revised Notice of Award. Additional work including filing a notice of Federal intent, Department of Labor and Industry accessibility variance hearings were conducted, and CM-at–risk proposal and sub contract proposals were signed. In August Penn State issued The Notice to Proceed to Torcon, Inc. Foundation excavation began in November 2011.

In addition, we hired a scientific director to oversee the research mission of the facility. Girish Kirimanjeswara is a faculty member with ABSL3 experience who will bring research experience and leadership to the facility. John Henneman has also been hired as the BRL manager. John has 15 years of experience overseeing the construction and operation of BSL3 facilities. He will oversee the construction of the facility, start-up, validation and commissioning, as well as maintenance and operations once the facility is built.

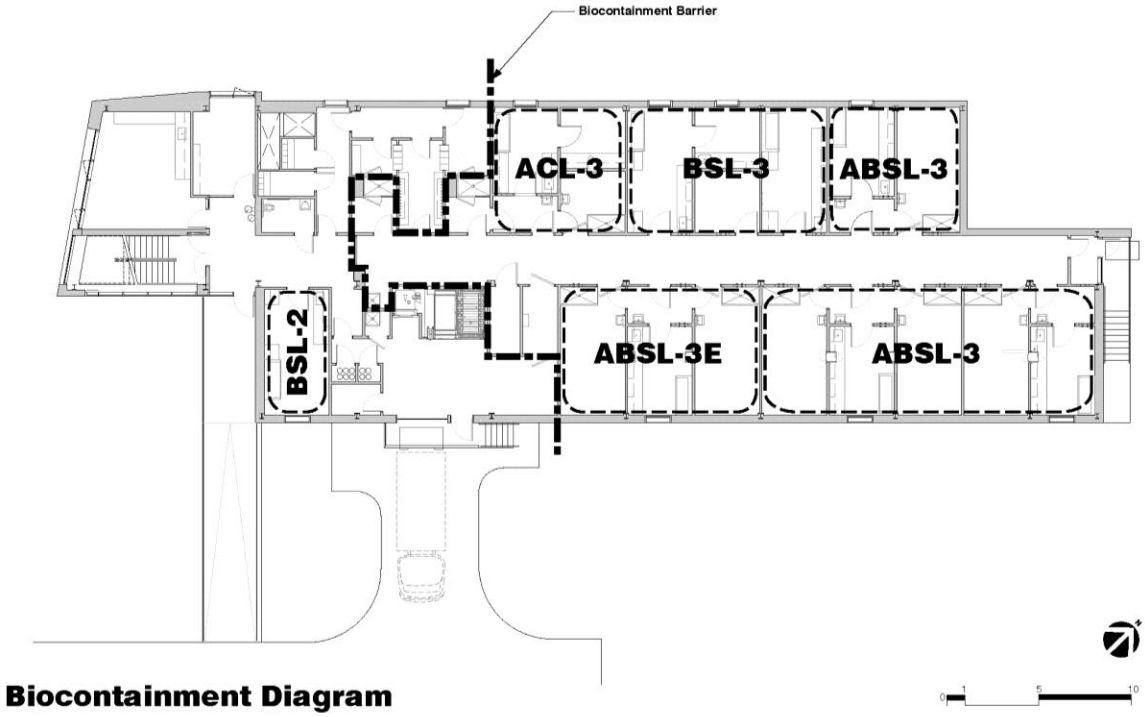

Figure 2._ Containment zones for the ABSL-3 facility include the insectary (arthropod containment level-3 (ACL-3), Biosafety Level 2 and 3 (BSL-2 and BSL-3) laboratory space, and Animal biosafety level-3 (ABSL-3) and enhanced ABSL-3 (ABSL-3E) space.

Figure 3. An artist's rendering of the BRL, showing the main personnel entrance and loading dock.

Much progress was made in 2012. Major concrete work was completed by February 2012. Sanitary system tie-ins, connections to campus water, and the site electrical underground duct bank were also completed (Figure 4). Building steel connections to the roof required extra coordination which postponed the start of steel work until May 2012, but the steel framing and most of the major concrete slabs were complete by July (Figures 5 and 6). Major equipment was then delivered and set to include; the hot water heaters, storage tanks, filter and softener. The emergency generator was delivered to the vendor's yard for testing and integration of the Automatic Transfer Switch. The primary transformer was set in the utility yard. The Effluent Decontamination System was delivered and set (Figure 7). Major framing and metal wall panels were installed and the roof deck was nearly complete (Figure 8). The mechanical piping and ductwork in the basement was completed. The plumbing subcontractor completed the stainless steel vent pipe in the penthouse. The electrical subcontractor completed the basement in wall rough in. By August major mechanical equipment was set in the penthouse to include, the air handling units and HVAC pump skids, also, the chillers were set in the utility yard.

In September, the boilers were delivered and placed in the basement. The lab HEPA filters were delivered. Interior partition drywall was complete in the basement, with the prime coat of paint complete. During October the building withstood the effects of Hurricane Sandy well. The site was prepared, policed and secured. Only minor replacement of some building paper was required on the south roof face. The site work subcontractor graded and stoned the north road and asphalt based the south road. They finish graded and spread topsoil on the eastern portion of the site. The building enclosure was progressing. The exterior window frames and glass are complete; masonry is 90% complete. Metal wall panels are 50% complete, the northwest, west, and south west walls are done. Work continued on interior drywall installation (Figure 9) and a special coatings mock-up was constructed to work out details for finishes and sealants at all penetrations. Work continued on the ductwork and piping along with the electrical rough-in in the lab area. The building controls subcontractor nearly completed lab rough-in. The HEPA units were set in place and the project team began bi-weekly commissioning meetings. By November, the building was nearly enclosed. All windows were installed, masonry was complete and a majority of the metal roof installed (Figure 10). Drywall partitions throughout the building were nearly complete and ceiling framing had begun. Work on the ductwork, piping, and insulation were nearly 80% complete, while the electrical rough-in was about 95% complete.

The main switchgear was energized (Figure 11) and the generator and transfer switch tested, with final commissioning to occur in the spring. This enabled the temporary electric heat system. The main entry conduit system was modified for architectural conformity as directed. December found the metal wall panels completed; the standing seam metal roof complete and the flat panel roof complete on the east side and in progress on the west side. The exterior louvers were installed on the east and north sides. The interior partition drywall was complete in the basement. Level one partitions were 98% complete with framing and drywall installed. Ceiling framing and drywall was complete in three suites. A special coatings mockup was completed. The wall and ceiling joints were being prepared for the special coating contractor. The EDS room wall coatings were complete. The mechanical piping and ductwork in the basement was 95% complete. The boilers and de-aerator are set and piped and ready for a preliminary inspection in early January. Steam station and pump skids were connected. The boiler room insulation was

90% complete. The penthouse ductwork and piping was 90% complete. The duct drops to the containment labs were 70% delivered and 30% installed. Duct testing was 50% complete. Penthouse HVAC insulation is still in progress. The Building Automation subcontractor was roughing in the penthouse.

The plumbing subcontractor was completing the water room piping. The containment corridor gas piping was complete awaiting valve box delivery. The electrical subcontractor was complete with the lab area rough in. Conductors were pulled through to the penthouse. The security conduit and panels were set. *See included milestone schedule page 21 for details on completion of the laboratory (Figure 12).* This schedule now shows the building interior compartments to be completed in late February, the site work to be completed in April, equipment start-ups completed in May and the commissioning completed by the end of June 2013. Building occupancy will officially begin in July with expected full operational status by the end of October 2013.

Figure 4. March 2012 - all major concrete work and basement underground plumbing is completed. View looking South.

Figure 6. June 2012 - Main floor, working on the pit for the autoclaves.

Figure 5. May 2012 - Steel frame nearly complete.

Figure 7. July 2012 -The Liquid effluent decontamination system is set in place.

Figure 8. August 2012- Roof deck complete as well as the exterior framing and sheathing

Figure 10. November 2012- Building enclosed and roof nearly complete

Figure 9. September- October 2012 - Interior partitions under construction

Figure 11. Main switchgear

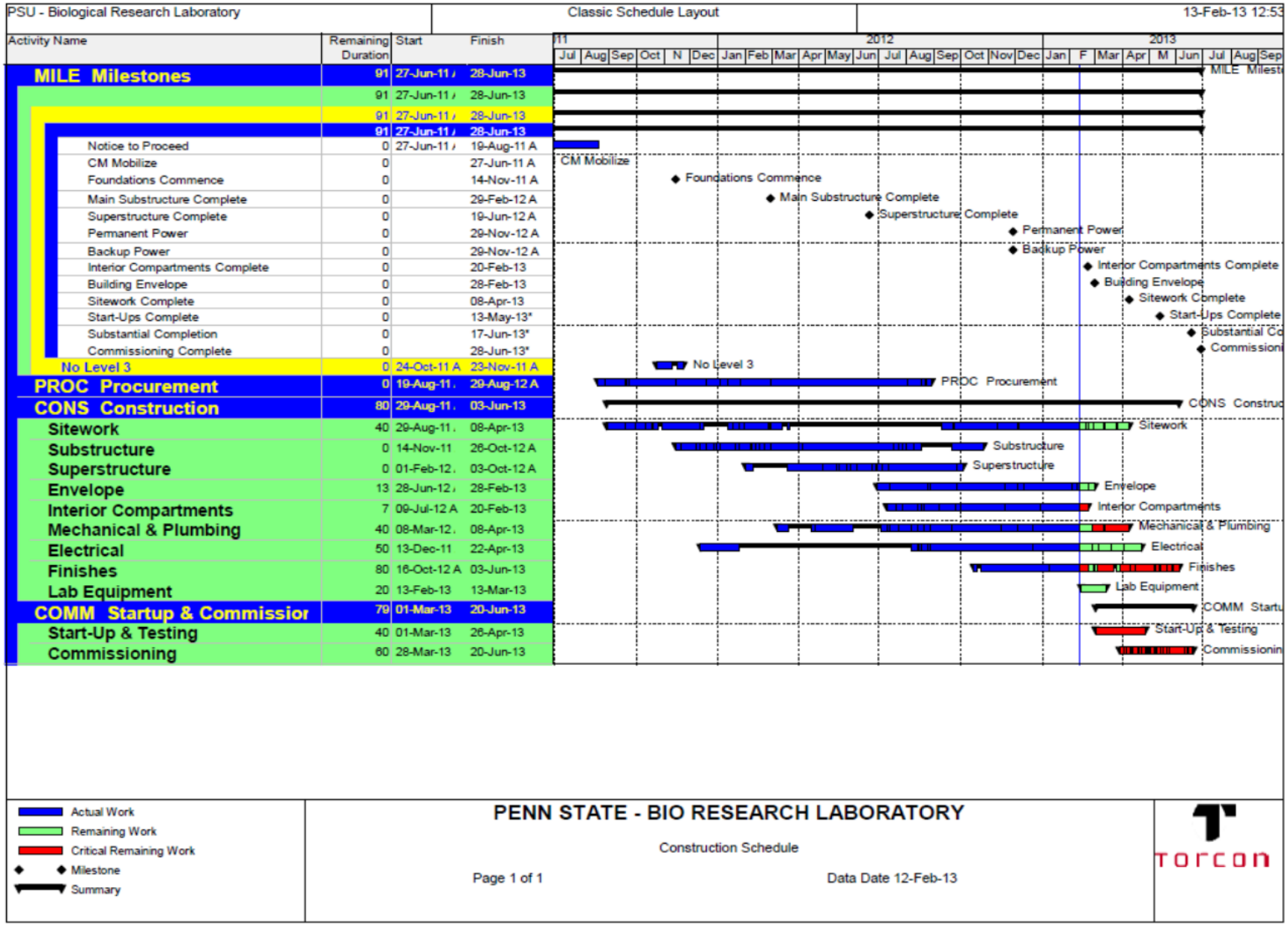

Figure 12. Schedule

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
__X___No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
__X___No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

_____Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

_____Number of subjects originally targeted to be included in the study
_____Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
_____Males
_____Females
_____Unknown

Ethnicity:
_____Latinos or Hispanics
_____Not Latinos or Hispanics
_____Unknown

Race:
_____American Indian or Alaska Native
_____Asian
_____Blacks or African American
_____Native Hawaiian or Other Pacific Islander
_____White
_____Other, specify:_____
_____Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
__X__ No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
____ No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, the number of the publication and an abbreviated research project title. For example, if you submit two publications for PI Smith for the "Cognition and MRI in Older Adults" research project (Project 1), and two

publications for PI Zhang for the "Lung Cancer" research project (Project 3), the filenames should be:

Project 1 – Smith – Publication 1 – Cognition and MRI
Project 1 – Smith – Publication 2 – Cognition and MRI
Project 3 – Zhang – Publication 1 – Lung Cancer
Project 3 – Zhang – Publication 2 – Lung Cancer

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. None				☐Submitted ☐Accepted ☐Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes____X___ No_____

If yes, please describe your plans:

Investigators using this facility will regularly submit their research findings to peer reviewed journals in the future.

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention,

diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No___x_____

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____
If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No___x

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes___ No___x

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No_____x_____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages. *For Nonformula grants only – include information for only those key investigators whose biosketches were not included in the original grant application.*

BIOGRAPHICAL SKETCH

NAME Kennett, Mary J.	POSITION TITLE Director, Animal Resource Program, Professor and Head, Dept. of Veterinary & Biomedical
eRA COMMONS USER NAME MKennett	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Washington State University	BS,	1981	Veterinary Science
Washington State University	DVM	1984	Doctor of Veterinary Medicine
Walla Walla College	MS	1987	Biology: Animal Behavior
University of Missouri	Residency	1998	Laboratory Animal Medicine
University of Missouri	PhD	1999	Pathobiology

Positions and Employment

1984-1987 Staff Veterinarian (mixed practice), Plaza Veterinary Clinic, Walla Walla, WA
1985-1987 Graduate Assistant Instructor (Cell Physiology, Anatomy), Walla Walla College, College Place, WA
1987 (summer)Visiting Professor (Biology for Educators), Whitman College, Walla Walla, WA
1988 -1989 Relief Veterinarian (part time) , Dayton Veterinary Clinic, Dayton, WA and Animal Clinic of Walla Walla, Walla Walla, WA
1988 (spring) Instructor (Comparative Physiology) , Walla Walla College, College Place, WA
1987-1989 Instructor (Anatomy & Physiology, Microbiology, Human Biology), Columbia Basin College, Pasco, WA
1989-1993 Tenured Instructor, Biology (Cell Biology, Zoology, Microbiology), Walla Walla Community College, (Cell Biology, Zoology, Microbiology), Walla Walla, WA
1993-1995 Molecular Biology Fellow, University of Missouri, Columbia, MO
1995-6/98 Lab. Animal Medicine Resident, University of Missouri, Columbia, MO
1998 –1999 Doctoral Candidate, University of Missouri, Columbia, MO
1999 – 2001 Assistant/Acting Director, OLAM, University of Missouri, Columbia, MO
2001 to present Director, Animal Resource Program Pennsylvania State University
2001 - 2007 Associate Professor, Dept. of Veterinary and Biomedical Sciences
2007 to present Professor of Veterinary & Biomedical Sciences, University Park, PA

Honors, Memberships, and Awards
Member of AVMA, ACLAD, ASLAP and ACLAM, National and Central PA AALAS, Phi

Kappa Phi, and the C. L. Davis Foundation for the advancement of veterinary and comparative pathology
2000 Diplomate, American College of Laboratory Animal Medicine

C. 15 Selected Peer-Reviewed Publications

1. Sae-Tan, S., Grove, K.A., **Kennett, M.J**., Lambert, J.D. Epigallocatechin-3-gallate increases the expression of genes related to fat oxidation in the skeletal muscle of high fat-fed mice. *Food Funct.* 2011 Feb;2(2):111-6. Epub 2011 Jan 4. PubMed PMID: 21779555.
2. Hegde, S., Kaushal N., Ravindra, K.C., Chiaro, C., Hafer, K.T., Gandhi, U.H., Thompson, J.T.,Vanden Heuvel, J.P., **Kennett, M.J.**, Hankey, P., Paulson, R.F., Prabhu, K.S. {Delta}12-prostaglandin J3, an omega-3 fatty acid-derived metabolite, selectively ablates leukemia stem cells in mice. *Blood*. Epub ahead of print. PubMed PMID: 21967980.
3. Zhu B., Bai R., **Kennett M.J.**, Kang B.H., Gonzalez F.J., Peters J.M. Chemoprevention of chemically induced skin tumorigenesis by ligand activation of peroxisome proliferator-activated receptor-beta/delta and inhibition of cyclooxygenase 2. *Mol Cancer Ther*. 2010 Dec;9(12):3267-77.
4. Markell, L.M., Pérez-Lorenzo, R., Masiuk, K.E., **Kennett, M.J., Glick, A.B.** Use of aTGF{beta}1 Type I Receptor Inhibitor in Mouse Skin Carcinogenesis Reveals a Dual Role for TGF{beta}1 Signaling in Tumor Promotion and Progression. *Carcinogenesis*. 2010 Sep 17. [Epub ahead of print] PubMed PMID: 20852150.
5. Li, P., Li, M., Lindberg, M.R., **Kennett, M.J.,** Xiong, N., Wang, Y. PAD4 is essential for antibacterial innate immunity mediated by neutrophil extracellular traps. *J Exp Med*. 2010 Aug 30;207(9):1853-62.
6. Lambert, J.D., **Kennett, M.J**., Sang, S., Reuhl, K.R., Ju, J., Yang, C.S. Hepatotoxicity of high oral dose (-)-epigallocatechin-3-gallate in mice. *Food Chem Toxicol*. 2010 Jan;48(1):409-16.
7. Wolfe, D.N. , Karanikas, A.T. , Hester, S.E. , **Kennett, M.J.,** and Harvill, E.T. IL-10 induction by *Bordetella parapertussis* limits a protective IFN-gamma response. *J Immunol.* 2010 Feb 1;184(3):1392-400. Epub 2009 Dec 30. PubMed PMID: 20042578
8. Bility, M.T., Devlin-Durante, M.K., Blazanin, N., Glick, A.B., Ward, J.M., Kang, B.H., **Kennett, M.J.**, Gonzalez, F.J., Peters, J.M. (2008) Ligand activation of peroxisome proliferator-activated receptor beta/delta (PPAR beta/delta) inhibits chemically induced skin tumorigenesis. Carcinogenesis. Dec;29(12):2406-14. PMID: 18799709
9. Shan, W., Palkar, P.S., Murray, I.A., McDevitt, E.I., **Kennett, M.J.,** Kang, B.H., Isom, H.C., Perdew, G.H, Gonzalez, F.J., Peters, J.M.. (2008) Ligand Activation of Peroxisome Proliferator-activated Receptor-{beta}/{delta} (PPAR{beta}/{delta}) Attenuates Carbon Tetrachloride Hepatotoxicity by Down-regulating Pro-inflammatory Gene Expression. *Toxicol Sci.* Oct;105(2):418-28. PMID: 18622026
10. Shan, W., Nicol, C.J., Ito, S., Bility, M.T., **Kennett, M.J.,** Ward, J.M., Gonzalez, F.J., Peters,J.. (2008) Peroxisome proliferator-activated receptor-beta/delta protects against chemically induced liver toxicity in mice. *Hepatology*. Jan;47(1):225-35. PMID: 18038451
11. Loving, C.L., **Kennett, M**., Lee, G.M., Grippe, V.K., Merkel, T.J. (2007). Murine aerosol challenge model of anthrax. *Infect Immun*. 2007 Jun;75(6):2689-98. PMID: 17353290
12. Hollingshead, H.E., Morimura, K., Adachi, M., **Kennett, M.J.**, (2007). Billin, A.N., Willson, T.M., Gonzalez, F.J., Peters J.M. PPAR β/δ Protects Against Experimental

Colitis in a Ligand-Independent Fashion. *Dig Dis Sci. 2007 Nov;52(11):2912-9.* PMID: 17404849

13. Tompkins, S.M., Lin, Y., Leser, G.P., Kramer, K.A., Haas, D.L., Howerth, E.W., Xu, J., **Kennett, M.J.,** Durbin, R.K., Durbin, J.E., Tripp, R., Lamb, R.A., He, B. (2007) Recombinant parainfluenza virus 5 (PIV5) expressing the influenza A virus hemagglutinin provides immunity in mice to influenza A virus challenge. Virology. May 25;362(1):139-50. PMID: 17254623
14. Hays, T., Rusyn, I., Burns, A.M., **Kennett, M.J**., Ward, J.M., Gonzalez, F.J., and Peters, J.M. (2005). Role of peroxisome proliferator-activated receptor-alpha (PPAR alpha) in bezafibrate-induced hepatocarcinogenesis and cholestasis. *Carcinogenesis* Jan; 26 (1):219-227. Epub 2004 Sep 24. PMID: 15447978

Kim, D.J., Akiyama, T.E., Harman, F.S., Burns, A.M., Shan, W., Ward, J., **Kennett, M.J**., Gonzalez, F.J.(I), and Peters, J.M.(PI). (2004). Peroxisome proliferator-activated receptor beta (delta)-dependent regulation of ubiquitin C expression contributes to attenuation of skin carcinogenesis. *J. Biol. Chem.* May 28; 279 (22):23719-27. Epub 2004 Mar 19 PMID: 15033975