IBC Meeting Minutes
April 17, 2025 (Thursday) at 11:00 A.M.
via Zoom Conference Bridge

IBC members present:

Tom Greenough (Chair)	X	Shaoguang Li		Carol Schrader	X	Edward Jaskolski (alt)	X
Lisa Cavacini	X	Philip Tai		Mohan Somasundaran		Timothy Kowalik (alt)	
Colleen Driskill	X	Robert Klugman		Richard Ellison III (alt)		Regino Mercado-Lubo (alt)	X
Kris Giaya	X	Amelia Houghton		Sharone Green (alt)		Casey Moran (alt)	X
Hardy Kornfeld		Eric Rouse	X	Jennifer Wang (alt)			

Non-members present: Patrice Rando (IACUC/IBC Office), Elizabeth Nadeau (IACUC/IBC Office)

I. Introductory Remarks

1) The Chair brought to the attention of the Committee the action items completed since the previous meeting and those submissions still under review by IBC.
2) The Chair brought to the attention of the Committee the meeting minutes from the previous IBC meeting. **Meeting Decision: Vote to approve March 20, 2025 Meeting Minutes**
3) DURC/PEPP policy go-live 05/06/2025
4) IBC Minutes public posting go-live 06/01/2025

II. Report on incidents/accidents from Employee Health Services (EHS)

1) 3/17/2025- Needle stick with xenograft with human cells. Source of human cells tested negative for BBP - Closed
2) No other lab incident relevant to IBC oversight

III. Protocols Reviewed Administratively

1) Investigator: Kim, S
Title: Imaging Neural Markers of the Infant's Social Engagement in the First Year of Life
IBC Registration: 757-25, Renewal
Training Verification: Acceptable pending completion of PI training
Brief Summary: Establish the relationship at 6 months between the infant's maternal cue reactivity (MCR) and the infant's social engagement with the mother. Examine the association between early mother-infant synchrony at 4 months and the infant's MCR at 6 months. Assess the extent to which MCR at 6 months is predictive of the development of infant attachment at 1 year. Involves measuring salivary oxytocin.

2) Investigator: Gounis, M
Title: Ex Vivo Modeling of Cerebral Emboli Mimicking Clots
IBC Registration: 758-25, Renewal
Training Verification: Acceptable
Brief Summary: To evaluate the recanalization efficacy of thrombectomy devices, a cerebral embolus mimicking clot model is required to create an occlusion simulating an ischemic stroke in-vitro.

In the treatment of ischemic strokes FDA-cleared devices may be used to recanalize the occluded vessel mechanically, and it is found that the success of the treatments is related to the composition and stiffness of the clots. Involves collection and analysis of resected atrial tissue and thrombus. Involves flow sorting, cell culture, cores for Light microscopy, EM, Cryo-EM and Proteomics

3) Investigator: Nguyen, T
Title: Acquisition of skin, bone, blood, and photograph of wounds from patients with diabetic foot ulcers for the investigation of mechanisms on how the diabetic immune system responds to wound healing
IBC Registration: **767-25, Renewal**
Training Verification: Acceptable
Brief Summary: We will obtain skin, bone, blood, and photograph of wounds from subjects with diabetic foot ulcers in order to investigate how the immune system mediates wound healing in diabetes.

IV. Protocols to Discuss

1) Investigator: Benanti, J
Title: Mechanisms of Cell Cycle Control
IBC Registration: **447-25, Renewal**
Training Verification: Acceptable
Brief Summary: The goal of this project is to understand the regulatory network that controls the cell cycle in budding yeast and human cells. Our work aims to investigate the contributions of transcriptional regulation, and phosphorylation to the cell cycle network. We will do this using genetics, biochemistry and cell biology.

Brief Summary and Review by Primary Reviewer

Overview and Objectives: The objectives of this project are to 1. Understand the regulatory network that controls the cell cycle in budding yeast and human cells 2. Investigate the role of transcriptional regulation and phosphorylation in cell cycle network

Experimental Approach: To accomplish these objectives, PI will employ 1. Genetics, Biochemistry and Cell biology approaches 2. Budding yeast and/or mammalian cells will be genetically manipulated using expression vectors constructed using E coli a. For budding yeast, experiments will involve expressing genes from a plasmid or by integrating mutations/epitope tags (PCR products) by homologous recombination b. For human fibroblast (HFF) or epithelial (U2OS) cell lines, transfection of expression plasmids or transduction using replication-deficient retroviruses or lentiviruses, or CRISPR-based mutational insertion will be used 3. Gene knock-down in human cells will be achieved by siRNA transfection or shRNA transduction 4. Cells will be processed for molecular biology analyses with TRIZOL-extracted nucliec acids, chromatin immunoprecipitation or immunofluorescence, and Western blot analysis of extracted proteins PI will be following BSL-2 biosafety protocols during transfection, transduction and subsequent experiments

IBC Discussion and Vote

Discussion: The reviewer mentioned this was first approved in 2010 at BSL-2 and twice renewed at BSL-2. The reviewer discussed that the species of yeast was not specified.

Meeting Decision: Vote to approve upon completion of action items.
BSL/ABSL: **BSL-2**
NIH Guidelines: III-D, III-E, III-F

2) Investigator: Bucci, V
Title: Microbiota community modulation via antibiotic and microbial mediated intervention
IBC Registration: **753-25, Renewal**
Training Verification: Acceptable pending completion of PI training
Brief Summary: The goals of the projects are: 1) Determine the effect of bacteriocins (specifically siderophore antimicrobial peptides) that are naturally encoded by gut bacteria in inhibiting drug-resistance *Enterobacteriaceae*. The project involves the construction recombinant *E. coli* strains that overexpress genes for the production and purification of these bacteriocins. 2) Determine the effect of microbiome modulation strategies in protecting from *C. difficile* infection. 3) Determine role of specific gut microbes in modulating host immune systems dynamics and neuro-cognitive behaviors

Brief Summary and Review by Primary Reviewer

Overview and Objectives: 1) Determine the effect of bacteriocins (specifically siderophore antimicrobial peptides) that are naturally encoded by gut bacteria in inhibiting drug-resistance Enterobacteriaceae. 2) Determine the effect of microbiome modulation strategies in protecting from C. difficile infection. 3) Determine role of specific gut microbes in modulating host immune systems dynamics and neuro-cognitive behaviors

Experimental Approach: 1) construction of recombiant E. coli strains that overexpress genes for the production and purificaiton of bacteriocins and testing in vitro; (2) and (3) in vivo mouse models

IBC Discussion and Vote

Discussion: Reviewer discussed this lab is very experienced with handling C. difficile and there is great attention to detail in safe handling, accidental exposure plan and treatment plan. A committee member raised the question regarding the potential for pathogens to be transmitted to other animals via water training or behavioral training caging and that this risk should be reflected in the decontamination practices of behavioral training facilities.
Meeting Decision: Vote to approve upon completion of action items.
BSL/ABSL: **BSL-2; ABSL-2**
NIH Guidelines: III-D, III-E, III-F

3) Investigator: Hayward, L
Title: A Phase 1/2, Open-label, Dose-escalation Study to Evaluate the Safety, Tolerability, and Biological Activity of EPI-321, an AAVrh74-delivered Epigenetic Editing Therapy in Adult FSHD Patients
IBC Registration: **917-25, New**
Training Verification: Acceptable
Brief Summary: Facioscapulohumeral muscular dystrophy (FSHD) is a degenerative muscle disease caused by a contraction of the D4Z4 macrosatellite repeat region on the subtelomeric long arm

of chromosome 4. This contraction leads to a loss of methylation of the region and a leaky and abnormal expression of a gene called the *DUX4* retrogene.

EPI-321 is an investigational drug product comprising a recombinant adenoassociated viral vector, serotype rh74 (AAVrh74), for the delivery of genetic material CK8e-dCasONYX-KLb_hU6-D4Z4gRNA encoding an epigenetic editing system. The transgene product is a non-cutting, nuclease-dead miniCRISPR-associated protein (dCasONYX) with an associated epigenetic modulator (KLb) designed to selectively bind the D4Z4 repeat region via the accompanying guide RNA (gRNA), methylate CpG groups within the region near the DUX4 gene, and thus repress the expression of toxic DUX4 protein. EPI-321 will be supplied by EpiCrispr Biotechnologies.

The objectives of this clinical study are to:

- To determine the safety and tolerability of EPI-321 over time
- To assess target engagement, biological activity, and preliminary efficacy of EPI-321

Brief Summary and Review by Primary Reviewer

Overview and Objectives: Facioscapulohumeral muscular dystrophy (FSHD) is a degenerative muscle disease caused by a contraction of the D4Z4 macrosatellite repeat region on the subtelomeric long arm of chromosome 4. This contraction leads to a loss of methylation of the region and a leaky and abnormal expression of a gene called the DUX4 retrogene. EPI-321 is an investigational drug product comprising a replication defective, recombinant adenoassociated viral vector, serotype rh74 (AAVrh74), for the delivery of genetic material CK8e-dCasONYX-KLb_hU6-D4Z4gRNA encoding an epigenetic editing system. The transgene product is a non-cutting, nuclease-dead miniCRISPR-associated protein (dCasONYX) with an associated epigenetic modulator (KLb) designed to selectively bind the D4Z4 repeat region via the accompanying guide RNA (gRNA), methylate CpG groups within the region near the DUX4 gene, and thus repress the expression of toxic DUX4 protein. EPI-321 will be supplied by EpiCrispr Biotechnologies.
The objectives of this clinical study are to: 1) To determine the safety and tolerability of EPI-321 over time; 2) To assess target engagement, biological activity, and preliminary efficacy of EPI-321

Experimental Approach: EPI-321 is a non-self-replicating AAVrh74 vector containing a single-stranded DNA encoding a muscle-specific CK8e promoter-driven dCasONYX (a mini catalytically inactive Cas protein), an engineered KRAB Domain-Methyl Transferase, and a gRNA targeting the D4Z4 region, including near the DUX4 gene, under the expression of the hU6 promoter. The payload is flanked by AAV2 inverted terminal repeats (ITRs), and the total ITR to ITR size is 4,540 base pairs.
Patients will be selected for the study based on specific eligibility criteria pertaining to safety measures and disease characteristics. Prior to receiving the therapy, they will be given oral prednisone for 3 days. The investigational therapy will be administered via a single intravenous infusion (2.0x10^13 vg/kg or 4.0x10^13 vg/kg) in an in-patient setting followed by a 48hr in-patient observation and subsequent follow-up visits to the research center over 5 years. Bloodwork will be performed prior to receiving therapy as well as during follow-up visits. Safety and tolerability of the therapy will be determined by the occurrence of adverse events as well as physical exams, ECHO, ECG, and lab testing (blood, urine, saliva). Shedding of vector, immune responses to vector, target engagement and transgene expression levels and methylation levels will be assessed (blood and muscle biopsies). Efficacy of the therapy will be determined by pulmonary function measures, functional measures, muscle strength, range of motion assessments, and physician and participant scores of disease severity.
Processing of human samples will occur in the Clinical Research Center lab under IBC registration I-631-20 (Luzuriaga). The product will be prepared for infusion in the UMass Investigational Drug Services (IDS) research pharmacy. Administration of the product will occur in-patient, 4th floor of UMass Memorial University Campus. Collection, processing, and storage of human samples will occur within the clinical research center (ACC building, first floor).

IDS staff will prepare the product in an appropriate biosafety cabinet and have internal SOPs regarding training of staff for each investigational product they dispense which includes review of the investigator brochure regarding drug risks. Research staff will oversee the infusion of the investigational drug and are trained in how to respond to spills.

IBC Discussion and Vote

Discussion: Reviewer discussed that they don't provide much information on the risks in the registration however, there are risks mentioned in the informed consent so this should be addressed. The protocol is awaiting review by the Gene and Cell Therapy Committee.
Meeting Decision: Vote to approve upon completion of action items.
BSL/ABSL: **BSL-2**
NIH Guidelines: III-C, III-E

4) Investigator: Newburger, P
Title: Function and Differentiation of White Blood Cells
IBC Registration: **209-25, Renewal**
Training Verification: Acceptable
Brief Summary: Our laboratory studies disorders of white blood cell number and function, with a focus on severe congenital neutropenia. We study the pathobiology of neutropenia due to mutations in the endosomal/lysosomal transport protein VPS45 in mouse models developed by CRISPR/Cas9-mediated knock-in of disease-causing mutations, We are also studying the use of CRISPR/Cas9-mediated gene knockout for treatment of severe congenital neutropenia due to dominant mutations in the *ELANE* gene encoding neutrophil elastase, using both primary human CD34+ stem/progenitor cells and myeloid cell lines.

Brief Summary and Review by Primary Reviewer

Overview and Objectives: To study disorders of white blood cell number and function, with a focus on severe congenital neutropenia. To study the pathobiology of neutropenia due to mutations in the endosomal/lysosomal transport protein VPS45 in mouse models developed by CRISPR/Cas9-mediated knockin of disease-causing mutations, To study the use of CRISPR/Cas9-mediated gene knockout for treatment of severe congenital neutropenia due to dominant mutations in the ELANE gene encoding neutrophil elastase, using both primary human CD34+ stem/progenitor cells and myeloid cell lines.

Experimental Approach: VPS45 neutropenia studies utilize mice developed in the UMMS Animal Modeling Core, with colonies maintained on campus. Mouse blood and tissues are used for analysis by flow cytometry, light and electron microscopy, western blotting, and RT-PCR. Similar assays are used on human peripheral blood cells, stem/progenitor cells and myeloid cells derived from them by in vitro culture, and myeloid cell lines obtained from ATCC. Microbial killing assays use non-pathogenic strains of gram negative bacteria. Flow cytometric sorting and analysis (in Core) of fixed and unfixed human peripheral blood and CD34+-cell-derived myeloid cells and mouse peripheral blood and bone marrow cells. Flow core sorting and analysis will be BSL-2, except for experiments using unfixed human cells, from tested donors, which will be BSL-2 enhanced. Light or electron microscopy; only of fixed mouse and human cells.

IBC Discussion and Vote

Discussion: The reviewer discussed that this protocol has been in used since 2005. The reviewer discussed that they are no longer listing that Staph auris and EBV are being used. If they are no longer in use, are they in storage.
Meeting Decision: Vote to approve upon completion of action items.
BSL/ABSL: **BSL-2; BSL-2 Enhanced Flow Sorting; ABSL-1**
NIH Guidelines: III-E, III-F

5) Investigator: Rhind, N
Title: Regulation of Yeast DNA Replication
IBC Registration: **276-25, Renewal**
Training Verification: Acceptable
Brief Summary: The lab studies the regulation of DNA replication in yeast. The goal is to understand how DNA replication is organized to ensure efficient and robust genome duplication.

Brief Summary and Review by Primary Reviewer

Overview and Objectives: The lab studies the regulation of DNA replication in yeast. Their goal is to understand how DNA replication is organized to ensure efficient and robust genome duplication.

Experimental Approach: The lab uses yeast genetics, molecular biology, and cell biology. They build plasmids in E. coli and transform them into yeast. They study the phenotypes of the transformed yeast using standard genetic, molecular, and cell biological assays.

IBC Discussion and Vote

Discussion: Reviewer discussed that it was first reviewed in 2005. No real changes were made to registration over the years.
Meeting Decision: Vote to approve upon completion of action items.
BSL/ABSL: **BSL-1**
NIH Guidelines: III-E, III-F

6) Investigator: Sluss, H
Title: Analysis of Tumor Suppressor Proteins
IBC Registration: **309-25, Amendment**
Training Verification: Acceptable pending completion of PI training
Brief Summary: We will utilize the Lyme spirochete as a study of the p53 pathway in infection and innate immunity. We will propagate Borrelia burgdorferi in the BSL2+ facility, to then introduce in animals in the A-level Bsl2. Personal generating the Spirochete will need to have training in the BSL2+ facility.

Brief Summary and Review by Primary Reviewer

Overview and Objectives: The objectives of this project are to examine the function of tumor suppressors in 1) cell cycle 2) growth arrest 3) senescence 4) genome instability 5) DNA repair and 6)control of metabolism.The Sluss Lab utilizes genetic engineered mice and tissue culture models to understand the ATM-ATR-p53 pathway function. They have generated mice bearing point mutations in the p53 tumor suppressor, and are working toward generating

mutations in p53 in cells using the Crispr/Cas9 system. In this amendment, they are introducing Borrelia burgdorferi in vitro and in vivo models of infection.

Experimental Approach: They will utilize Borrelia burgdorferi infections as a model to study the role of the p53 pathway in infection and immunity . Borrelia burgdorferi will be propagated in a BSL2+ facility. Mice will be infected via intraperitoneal injection.

IBC Discussion and Vote

Discussion: Reviewer discussed action items.
Meeting Decision: Vote to approve upon completion of action items.
BSL/ABSL: **BSL-2; BSL-2 Enhanced Sorting; ABSL-2**
NIH Guidelines: N/A

7) Investigator: Swain, S
Title: Immune Response of B and T Cells
IBC Registration: **441-25, Renewal**
Training Verification: Acceptable
Brief Summary: Our laboratory seeks to understand the mechanisms that underlie the generation, maintenance and function of CD4 and CD8 T effector and memory T cells and B cells, and the various roles that they play in response to different pathogens in general and in the response to influenza infection in particular. These studies also include how these immune functions change in aging.

Brief Summary and Review by Primary Reviewer

Overview and Objectives: To understand the mechanisms that underlie the generation, maintenance and function of CD4 and CD8 T effector and memory T cells and B cells, and the various roles that they play in response to different pathogens in general and in the response to influenza infection in particular. These studies also include how these immune functions change in aging.

Experimental Approach: 1) Naïve donor cells are injected intravenously (IV) in small numbers (less than 106 per mouse). The host responds normally to a sublethal dose of live IAV that is introduced by the intranasal route to best mimic normal infection. All influenza viruses used, including viral recombinants and mutants, are from highly characterized stocks that we have been using for 10 years or more. 2) In some cases non-living vaccines composed of viral proteins with or without adjuvants that mimic viral pathogen-associated molecular patterns (PAMP) are used. mRNA vaccines and LNP may be administered to mice. Proteins generally cause a muted response, while adjuvants cause modest systemic inflammation. We routinely monitor systemic inflammation in key studies. 3) The generation of memory is determined by assessing the representation of donor memory cells by flow cytometry (using the identifying markers (e.g.for B cells: CD93,CD80/86 for T cells:CD90, CD45,) and determining their ex-vivo development of antibody-secreting cells (AbSC)(B cells) and cytokine production and cytotoxic and helper activity phenotypes (T cells) after re-exposure to antigen. Memory cells are also assessed in vivo by challenge of mice bearing memory with higher virus doses that would be lethal in unimmunized mice but are not lethal when CD4 memory cells are present. Assessments are done 2-60 weeks after initial infection. All infected mice are housed in isolator cages, and manipulated in microisolator. Virus work will be performed in the Biocontainment Suite in the Department of Animal Medicine.

IBC Discussion and Vote

Discussion: Reviewer discussed that they didn't describe the experiments being done with both retrovirus or oncogenes. The reviewer raised the question of SARS CoV2 being kept in storage or not as it was previously added but not included in this renewal.

Meeting Decision: Vote to approve upon completion of action items.

BSL/ABSL: **BSL-2; BSL-2 Flow Sorting; ABSL-2**

NIH Guidelines: III-D, III-E, III-F

8) Investigator: Wang, J
Title: Immune responses to viral infections
IBC Registration: **752-25, Renewal**
Training Verification: Acceptable
Brief Summary: These studies aim to define the role of viruses and host immune responses in the pathogenesis of autoimmune diabetes. Immune responses include innate (type I interferon, cytokines) and adaptive (MHC class I and II presentation to T cells).

Brief Summary and Review by Primary Reviewer

Overview and Objectives: These studies aim to define the role of viruses and host immune responses in the pathogenesis of
autoimmune diabetes. Immune responses include innate (type I interferon, cytokines) and adaptive (MHC class I and II presentation to T cells

Experimental Approach: In human type 1 diabetes (T1D), the immune system attacks β cells, the cells in the body that produce
insulin. Viral infections are implicated in the pathogenesis of T1D.
They propose to study how blocking inflammation with 12-lipoxygenase inhibition in human islets impacts β-cell function during infection with Coxsackievirus B (CVB) as an inducer of β-cell stress. They plan to study primary human islets,
human embryonic stem cell-β cells (PMID:25392246) and human pancreatic slices cultured in vitro to study the effects of virus infection and inflammatory inhibition at the single-cell level. Primary human islets will be obtained from cadaveric, non-diabetic samples from various external sources (e.g. Prodo Laboratories). Similarly, human pancreatic tissue will be studied as a mixed source of endocrine and non-endocrine cells in the context of viral infection. These tissues will be obtained from discarded, deidentified operating room (i.e., surgical) samples at UMMC through Drs. Greiner and Whalen. Human islets and pancreatic tissue will be studied in vitro.
CVB causes diabetes in mice dependent on engrafted primary human islets for glycemia control, decreasing human insulin levels, proving that virus infection can lead to human β-cell dysfunction in vivo (PMID:25392246). An established human islet-engrafted mouse model will be used for testing 12-lipoxygenase inhibitors in vivo.
The following control viruses that do not induce β-cell stress or human islet inflammation will be tested: human cytomegalovirus, influenza A virus, vesicular stomatitis virus, encephalomyocarditis virus, and Sendai virus as controls in vitro. Some virus controls are recombinant, expressing fluorescent proteins to assist in observing the degree of infection of cells and various organs using fluorescence detection techniques such as flow cytometry and fluorescence microscopy. Lipopolysaccharide will be used as a positive control for induction of inflammation in vitro.
They are also using rat models in which challenge with the parvovirus Kilham rat virus (KRV) results in autoimmune diabetes (PMID:27999109). Immune cells and pancreatic sections will be harvested from this in vivo model (in which a specific virus induced diabetes) for further analyses by RNA-in situ hybridization, immunohistochemistry, and flow

cytometry, and also by single-cell RNA-Seq. The H-1 rat parvovirus, which is a non-diabetogenic virus will be used as control. By analyzing differences in the inflammatory immune responses elicited by KRV compared to H-1 virus, they will identify signaling pathways and specific genes that are crucial to the development of autoimmune diabetes and can target these for knockout.

IBC Discussion and Vote

Discussion:	Reviewer discussed the lab is very experienced and the renewal is well written. The risks were well described as well as the procedures in the event of an accidental exposure. The reviewer discussed that SARS CoV2 work has been removed from the renewal.
Meeting Decision:	Vote to approve upon completion of action items.
BSL/ABSL:	**BSL-2; BSL-2 Enhanced Sorting; ABSL-3**
NIH Guidelines:	III-D, III-E, III-F

V. Report on incidents/accidents/issues involving BSL-3 & ABSL-3 Facilities

1) Supply fan still being worked on at this time.

Dates to track:

2) BSL-3/ABSL-3: N/A

VI. Information from the field (Senior Biosafety Officer)

N/A

VII. Other Business

N/A

Acknowledgement Items:

1) Luzuriaga 871-23 "**A Phase I, Randomized, Observer-Blind, Placebo-Controlled, 2-Part, Dose-Ranging Study of an EBV Candidate Vaccine, mRNA-1195, in Healthy Participants 18 through 55 Years of Age"** Update to revise cohort enrollment
2) Caricchio 888-24 " **A Phase 1 Study of NKX019, a CD19 Chimeric Antigen Receptor Natural Killer (CAR NK) Cell Therapy, in Subjects with Autoimmune Disease"** Update to add new autoimmune condition
3) Ramanathan 907-24 **"Expanded Access Protocol (EAP) for Subjects Receiving Lisocabtagene Maraleucel that is Nonconforming for Commercial Release"** Update to revise safety information

Adjourned at 1:16pm