

Institutional Biosafety Committee:

Present: Dr. Steven Albelda, Dr. Julian Baptiste, Dr. Jessica Buchanan, Dr. Joseph Fraietta, Dorothy Kaplan, Dr. Daniel Kessler, Dr. Andrew Maksymowych, Dr. Maureen O’Leary, Dr. David Pegues, Ms. Jessa Yoos

Absent: Dr. Paul Bates, Dr. Sara Cherry, Ms. Denene Wambach

Invited Guests: Ms. Stephanie Adams, Dr. Sarah Capasso, Ms. Marie-Luise Faber, Dr. Tucker Piergallini, Ms. Amanda Wong, Ms. Kimberly Craig,

The Institutional Biosafety Committee Meeting was called to order by Dr. Daniel Kessler at **10:00 AM**.

1. IBC Minutes: **07-28-2025**

- The IBC reviewed the IBC Minutes.
- All members are in favor of approval as submitted.
- Minutes approved as submitted.

2. Registrations for Review:

SECTION III–C. Experiments Involving Human Gene Transfer that Require IBC & IRB Approval Prior to Initiation:

1. Bivalacqua..... #25-226C-1

Dr. Trinity Bivalacqua– NEW HGT Protocol Registration..... **FULL REVIEW**

PROTOCOL TITLE: A Phase 3b, Randomised, Controlled Trial of Nadofaragene Firadenovec vs. Observation in Subjects with Intermediate Risk (IR) Non-Muscle Invasive Bladder Cancer (NMIBC). (Protocol V5 dated February 27, 2025; Main ICF dated April 9, 2025.)

IBC #25-226, IRB #857776, IND #12547, Protocol #ABLE-32-000423

- Dr. Daniel Kessler introduced the submission.
- Dr. Steven Albelda provided a summary and analysis.

“Project Overview: The primary objective is to evaluate the efficacy of nadofaragene firadenovec (Ad.IFNalpha) administered every 3 months vs. observation in subjects with intermediate risk (IR) non-muscle invasive bladder cancer (NMIBC). Approximately 50% of subjects with IR NMIBC will experience recurrence. The use of maintenance treatment with nadofaragene firadenovec following tumor resection to prevent recurrence and progression may improve clinical outcomes in subjects with IR NMIBC. This is a multi-center, open-label, randomised phase 3b trial. The primary endpoint is recurrence-free survival (RFS), defined as the time from the date of randomization to first documented recurrence or progression (as defined in the below table), or death (due to any cause), whichever occurs first during the treatment period (24 months).

Agent Description: Nadofaragene firadenovec is a replication-deficient recombinant type 5 adenovirus vector containing the human interferon- α 2b (IFN- α 2b) gene. Further details were not provided, however the drug has been approved by the FDA for earlier stage bladder cancer.

Is a novel vector system, approach or technology used for this clinical trial? NO

Gene transfer agent delivery method: Injection into the bladder. 75 mL (3 x 10¹¹ vp/mL) of sterile suspension will be instilled quarterly into the bladder via a urinary catheter.

Intended target: Nadofaragene firadenovec is instilled quarterly into the bladder by intravesical instillation to deliver the IFN- α 2b gene into the urothelial lining of the bladder. Intravesical instillation of nadofaragene firadenovec takes advantage of the localised nature of bladder cancer to expose tumor cells to high concentrations of IFN- α 2b protein. High local concentrations of IFN- α 2b protein and increased duration of exposure are expected to potentiate durable therapeutic responses.

Other material to be used in preparation of the agent: An excipient called Syn3NODA will also be injected into the bladder. Syn3NODA enhances gene transfer across the urothelium.

Preclinical studies: Nadofaragene firadenovec was approved by the US FDA in 2022 for the treatment of adult patients with high-risk Bacillus Calmette-Guérin (BCG)-unresponsive NMIBC with CIS with or without papillary tumors.

Potential for shedding: Patients will be advised that shedding into urine can take place for 2 days and to appropriately dispose of urine.

Are “Standard Precautions,” Biosafety Level 2 (BSL-2) equivalent, practices appropriate for ensuring clinical trials personnel safety? YES

This Registration Meets IBC Criteria for Approval: YES. I recommend approval, as submitted.”

- The new HGT registration was discussed by the committee members.
- All members were in favor of approval.
- The new HGT registration is approved as submitted.

2. Chapin.....#25-175 C-1

Dr. William J Chapin – HGT Protocol Registration Amendment V3 **AMENDMENT**

PROTOCOL TITLE: UPCC 06225: Phase II study of neoadjuvant RP2 in combination with preoperative FLOT for patients with stage II or higher, non-metastatic gastroesophageal adenocarcinoma. (Protocol V3 dated June 27, 2025; Main ICF dated June 10, 2025.)

IBC #25-175, IRB #858613, IND #31637, Protocol #0306

- Dr. Daniel Kessler introduced the submission and provided a summary and analysis.

“Project Overview: This is a single-arm, phase II study using a Simon two-stage optimal design with a 6 patient safety run-in evaluating the addition of intra-tumoral injections of RP2 (modified, selectively replication competent, acyclovir-sensitive, herpes simplex virus type 1) to standard of care perioperative FLOT (iv 5-fluorouracil, leucovorin, oxaliplatin and docetaxel) for patients with stage II or higher, non-metastatic esophageal, gastroesophageal junction, or gastric adenocarcinoma. The investigators hypothesize that the addition of RP2 to perioperative FLOT will be safe and will significantly improve pathologic complete response rate compared to the historical weighted average of 12% observed with perioperative FLOT in prior trials. The study population will include up to 34 adult patients with newly diagnosed clinical T2 or higher or any node positive, non-metastatic esophageal, GEJ, or gastric adenocarcinoma that are eligible for perioperative FLOT followed by surgical resection. Patients must not have a contraindication to chemotherapy, oncolytic viral therapy or to repeat endoscopies for intra-tumoral injection of RP2.

Agent Description: RP2 is a selectively replication competent, acyclovir-sensitive, herpes simplex virus type 1 (HSV-1) that expresses exogenous genes and is administered by intratumoral injection. RP2 was constructed using a new strain of HSV-1 (strain RH018). The neurovirulence factor (ICP 34.5) encoding genes and the ICP47-encoding gene are deleted from the virus. The virus also contains a codon-optimized sequence for human granulocyte-macrophage colony-stimulating factor in addition to a codon-optimized sequence for the gibbon ape leukemia virus surface protein with the R sequence deleted. Cell-to-cell fusion is caused by GALV-GP-R-, resulting in accelerated cell death. Further, RP2 expresses a human cytotoxic T lymphocyte antigen 4 blocking antibody-like molecule (ahCTLA-4), which interferes with the interaction of cytotoxic T lymphocyte antigen 4 (CTLA-4) with B7 molecules on professional antigen presenting cells. RP2 is cultured in Vero cells (kidney epithelial cells from African green monkey) prior to collection and purification to prepare the investigational medicinal product. After purification, the final formulation is provided at 2 different concentrations of RP2 in a solution for injection consisting of phosphate buffered saline, myo-inositol, sorbitol, and recombinant human serum albumin (HSA) in water for injection (WFI). RP2 is provided as a sterile frozen liquid solution and should be stored between -90°C to -60°C prior to use.

Is a novel vector system, approach or technology used for this clinical trial? NO

Gene transfer agent delivery method: RP2 will be delivered by upper endoscopy with intra-tumoral injection into the esophageal, GEJ, or gastric primary tumor at a dose of up to 10mL of 1 x 10⁶ PFU/mL solution within 4 days prior to cycle 1 of FLOT followed by a dose of up to 10mL of 1 x 10⁷ PFU/mL solution within 4 days prior to each preoperative cycle of FLOT thereafter. Up to 4 doses of intratumoral injection of RP2 will be administered. Only the primary tumor will be injected; regional lymph nodes will NOT be injected with RP2. The maximum volume to be injected is based on largest tumor diameter of the primary tumor as assessed by the endoscopist by direct visualization and/or endoscopic ultrasound at the time of each upper endoscopy for intra-tumoral injection (1.0-10.0 mL).

Intended target: Target is the primary tumor in vivo.

Other material to be used in preparation of the agent: None. Virus is purified in preparation of the investigational product.

Potential for shedding: Viral shedding studies are currently ongoing. The highest copy numbers of RP2 DNA were observed in the blood shortly after injection (6 hours) with some patients showing continued presence throughout the 15 days until the next injection of RP2. This pattern suggests kinetics indicative of RP2 replication in tumors. Exterior of injection-site dressing tested positive in 2 of 3 patients (66.7%) and 8 of 28 samples (28.6%)

with low copy numbers of RP2 DNA compared with copy numbers detected at the injection sites. Low copy numbers of RP2 DNA were found in the oral mucosa of 2 of 3 patients (66.7%) and 6 of 40 samples (15%). During the safety follow up period, RP2 DNA was not detected at either 30 days or 60 days after the last RP2 dose in any samples. All swab samples that tested positive for RP2 DNA were further assessed for the presence of live virus, and all tested negative. To date, no RP2 DNA has been detected in swab samples collected from lesions that could potentially be herpetic in origin, and there have been no reports of herpetic infections in patients' caregivers. Additional testing is ongoing.

Are "Standard Precautions," Biosafety Level 2 (BSL-2) equivalent, practices appropriate for ensuring clinical trials personnel safety? YES

This Registration Meets IBC Criteria for Approval: YES. I recommend approval, as submitted."

- The amendment was discussed by the committee members.
- All members were in favor of approval.
- The HGT registration amendment is approved as submitted.

3. Dorgan#25-230 C-1

Dr. Daniel J Dorgan – NEW HGT Protocol Registration **FULL REVIEW**

PROTOCOL TITLE: A Phase 1 Study of Inhaled KB407, a Replication Defective, Non-Integrating Vector Expressing Human Cystic Fibrosis Transmembrane Conductance Regulator, for the Treatment of Cystic Fibrosis (Protocol V4 dated July 13, 2023; Main ICF dated July 7, 2025.)

IBC #25-230, IRB #858964, IND #28594, Protocol #KB407-02

- Dr. Daniel Kessler introduced the submission.
- Dr. Jessica Buchanan provided a summary and analysis.

"Project Overview: Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which encodes an epithelial anion channel protein that maintains the balance of chloride and fluid at the cell surface. The primary objective of this Phase 1 study is to assess safety and tolerability of nebulized KB407 in adults with CF. The sequential cohort design is intended to assess the safety of a starting dose of KB407, before progressing to ascending doses (split across several days to maintain nebulization sessions of <30 minutes each) to evaluate safety and preliminary efficacy. Secondary and exploratory endpoints are included to measure the effect of KB407 on pulmonary function (to provide assessment of preliminary efficacy) and to examine intermediary

mechanism of action assessments of vector transduction and transgene expression in buccal and bronchial samples. In conjunction with the safety and tolerability results, these secondary and exploratory endpoints will help guide study design for future studies of KB407. A mandatory bronchoscopy was included in Cohort 3 to assess expression of CFTR in the airways at the highest dose. A single bronchoscopy 24 to 96 hours after the last dose of IP was deemed to be sufficient for assessing mechanism of action, while also minimizing the number of interventional procedures.

Agent Description: KB407 is a replication-defective, non-integrating herpes simplex virus type 1 (HSV-1)-derived vector engineered to deliver functional full-length human CFTR directly to the patient's airways via nebulization. It's a non-replicating HSV-1-based vector modified as follows:

- Complete deletion of multiple viral Immediate Early (IE) genes, including Infected Cell Protein (ICP) 4, rendering the virus non-replicating and less cytotoxic.
- Inclusion of an expression cassette containing a human cytomegalovirus (HCMV) promoter-driven CFTR transgene construct inserted within both copies of the deleted ICP4 loci.

Is a novel vector system, approach or technology used for this clinical trial? YES

Gene transfer agent delivery method: HSV-1 viral vector administered via inhalation using an Aerogen Solo nebulizer, with the Aerogen Ultra accessory and USB controller. Patients will nebulize 8 mL of investigational product per administration, equivalent to a pulmonary dose of $\sim 1.9 \times 10^9$ plaque forming units per administration.

Intended target: Engineered to deliver *CFTR* directly to the patient's airways via nebulization.

Other material to be used in preparation of the agent: PBS + 5% glycerol.

Preclinical studies: Clinical data from the Sponsor's topically applied products with the same HSV-1 backbone as KB407 have demonstrated a favorable safety profile after repeat dosing of the Sponsor's gene therapy products. Results of the GLP toxicology study of KB407 in NHPs indicate that repeat dosing of KB407 was well tolerated and no adverse effects were seen at the highest feasible dose level. As KB407 will be the first inhaled administration of an HSV-1 vectored gene therapy, potential risks associated with KB407 in this study will be mitigated through: • Sequential enrollment of cohorts and staggered dosing of subjects • Data Monitoring Committee (DMC) oversight and review prior to initiation of Cohort 2 and Cohort 3 • Individual and cohort level safety stopping rules • Regular safety monitoring of the clinical data by the medical monitor/Sponsor • Collection of samples to evaluate any potential for vector shedding or development of antibodies to HSV-1 • Long term follow-up of subjects annually

after the last dose of KB407 (through a separate long term follow-up protocol) The potential unknown risks of KB407, as mitigated by the study design elements above and the clinical experience with the Sponsor's HSV-1 backbone products in other patient populations, are expected to be outweighed by the potential benefits to be gained from this Phase 1 study of KB407, and its future potential as an effective therapy for CF patients, regardless of genotype.

Potential for shedding: Shedding potential is presumed to be similar to other gene therapies, and monitoring is in place. Additionally, immunogenicity to HSV-1 is not expected to be a limitation in the clinical setting since HSV-1 is a human virus that is prevalent in over half the population. The retention of ICP47 in the vector backbone, and subsequent inhibition of loading of virus-specific peptides onto major histocompatibility complex (MHC) class I molecules upon cellular infection, reduces the potential for T-cell recognition of KB407. Additionally, because KB407 is nonreplicating, cell-to-cell infection is not feasible, and KB407 exposure to the extracellular space is minimized, which avoids interaction with existing humoral antibodies.

Are "Standard Precautions," Biosafety Level 2 (BSL-2) equivalent, practices appropriate for ensuring clinical trials personnel safety? YES

This Registration Meets IBC Criteria for Approval: YES. I recommend approval, as submitted."

- The new HGT registration was discussed by the committee members.
- All members were in favor of approval.
- The new HGT registration is approved as submitted.

4. Ellis#25-249 C-1

Dr. Colin A Ellis – NEW HGT Protocol Registration **FULL REVIEW**

PROTOCOL TITLE: A Multi-Center, Open-label, Phase 1/2 Trial of the Safety and Efficacy of MVX-220 Gene Therapy Administered by Intra-Cisterna Magna Injection to Participants with Angelman Syndrome (Protocol V2 dated May 13, 2025; Main ICF dated July 31, 2025.)

IBC #25-249, IRB #859094, IND #31411, Protocol #MVX-AAV-101

- Dr. Daniel Kessler introduced the submission.
- Dr. Joseph Fraietta provided a summary and analysis that was read into record by Dr. Andrew Maksymowych.

“Project Overview: MVX-220 is a non-replicating recombinant AAVhu68 vector carrying a codon-optimized human UBE3A isoform-1 cDNA under the human synapsin (hSyn) promoter with SV40 polyA, flanked by AAV ITRs. Single dose administered by CT-guided ICM injection under general anesthesia; target dose 6.67×10^{11} GC/g estimated brain weight. Product is a sterile suspension in a single-use vial, stored at -70°C to -90°C . Participants receive prophylactic glucocorticoids (Day -5 through ≥ 1 month, then taper). Biodistribution (blood, CSF) and shedding (urine, feces) vDNA are collected per SOA; immunogenicity (total & neutralizing anti-AAVhu68) assessed in blood/CSF.

Agent Description: 1. Product / Vector: MVX-220 (AAVhu68-hSyn-hUBE3A-1.GSco.SV40) non-replicating recombinant AAV.

2. Transgene: hUBE3A-1 (codon-optimized human ubiquitin protein ligase E3A, isoform 1).

3. Control elements: hSyn promoter (neuron-selective), SV40 polyA.

4. Other elements: 5'/3' AAV ITRs only; no wild-type AAV coding sequences retained.

5. Serotype/capsid: AAVhu68 neurotropic capsid; delivered to CSF via cisterna magna.

Is a novel vector system, approach or technology used for this clinical trial? YES

Gene transfer agent delivery method: CT-guided sub-occipital ICM injection using a 22–25 G Quincke needle; manual slow bolus at 1-2 mL/min. Total volume 8-16 mL based on MRI-derived brain weight (pediatric 8-12 mL; adult 10-16 mL). General anesthesia with intubation; contrast myelography as needed. Intended target:

Other material to be used in preparation of the agent: Diluent (sterile, artificial CSF-like): 150 mM NaCl, 3 mM KCl, 1.4 mM CaCl_2 , 0.8 mM MgCl_2 , 0.001% poloxamer 188 in 1 mM sodium phosphate, pH 6.4–7.6; stored -70°C to -90°C .

No helper virus or packaging at clinical site (finished product dispensed/prepared via pharmacy). Manufacturing / packaging cell line details are not specified in the protocol; refer to IB/CMC for QC (e.g., rcAAV, sterility).

Preclinical studies: AS mouse model: dose-dependent improvements (weight, nest building, motor learning) with brain UBE3A expression (WB/IF), supporting proof-of-concept. Class-wide AAV risks summarized in protocol; no defined DRG/sensory toxicity with MVX-220 in animals; human DRG risk monitored conservatively with NfL \pm nerve conduction.

Potential for shedding: Potential for shedding. Protocol collects vDNA for biodistribution (blood, CSF) and shedding (urine, feces); sampling stops once below LLOQ at or after Week 8 per matrix. AAV is non-replicating and integration risk is low (ITRs only), so overall public risk is low when standard precautions are followed. Provide

clear inpatient and take-home hygiene instructions for handling excreta (esp. diapered participants).

Other safety issues in protocol to track (class-wide risk): complement-mediated TMA/aHUS (early labs, GI prodrome), cardiomyopathy/myocarditis (rare), HLH/MAS, and malignancy surveillance (low integration risk; AESI if diagnosed). ICM procedural risks mitigated by imaging and technique; immunosuppression risks mitigated by taper and stress-dose coverage.

Are “Standard Precautions,” Biosafety Level 2 (BSL-2) equivalent, practices appropriate for ensuring clinical trials personnel safety? YES

This Registration Meets IBC Criteria for Approval: YES. I recommend approval, as submitted.

YES—with the suggested clarifications / conditions (below) to place in the approval letter.

1. Provide Pharmacy & Administration Manuals to IBC/EHS to confirm BSC use, PPE, spill response, disinfection chemistry, and waste handling specifics (protocol defers these details to manuals).
2. Submit manufacturing QC summaries to IBC file (e.g., rcAAV negativity, sterility/endotoxin) from IB/CMC/COA (not in protocol; would be nice to have on file).
3. Add explicit caregiver instructions for excreta handling at home (duration, gloves, double-bagging diapers/wipes, surface disinfection), harmonized with institutional SOPs; the protocol monitors shedding but does not spell out home hygiene guidance.
4. Confirm any post-dose restrictions (blood/organ donation; sexual activity/contraception). Pregnancy/lactation are exclusionary; post-dose guidance for donors/partners is not explicit in the protocol text reviewed.”

- The new HGT registration was discussed by the committee members.
- All members were in favor of approval.
- The new HGT registration is approved as submitted.

5. Tebas#22-239..... C-1

Dr Pablo Tebas– HGT Protocol Registration Amendment V11 **AMENDMENT**

PROTOCOL TITLE: Phase I, randomized, observer-blinded, placebo-controlled, 2-part, dose escalation and expanded safety evaluation trial to evaluate the safety, tolerability and immunogenicity of an investigational prophylactic vaccine for the prevention of genital lesions caused by HSV-2 and potentially HSV-1. (Protocol V11 dated May 15, 2025; Main ICF dated June 8, 2025.)

IBC #22-239, IRB #852362, IND #28577, PROTOCOL #BNT163-01

- Dr. Daniel Kessler introduced the submission.
- Dr. David Pegues provided a summary and analysis.

“Project Overview: Genital infection caused by HSV-2 affects 500 million people, and HSV-1 genital herpes affects more than 140 million people worldwide. No vaccine has been licensed for prevention of genital lesions caused by HSV to date despite extensive efforts by pharmaceutical companies evaluating various subunit vaccine candidates through to large Phase III trials.

This trial has three parts. Part A is a dose escalation part, Part B is an expanded safety and dose evaluation part, and Part C is a safety and immunogenicity evaluation part in individuals with recurrent HSV-2 genital herpes. A total of ~308 subjects are expected to enroll: ~48 subjects in Part A, ~200 subjects in Part B, and ~60 subjects in Part C. In Part B, subjects will be randomized 1:1 by baseline HSV-2 and HSV-1 serostatus to receive either 3 doses of 30 or 60 mcg of BNT163 HSV-2 RNA-lipid nanoparticle vaccine, the doses selected based on data from Part A. In part C, HSV-2+ subjects will be randomized 1:1 to receive either 3 doses of 30 or 60 mcg of BNT163 HSV-2 vaccine.

Version 11 of the study protocol was made for the following reasons:

- Addition of a new subsection to enable implementation of planned stepwise unblinding after the conclusion of each trial part.
- Addition of windows for the start and end of continuous antiviral therapy and for the corresponding reminder phone calls to increase flexibility.
- Correction of total blood volumes drawn.

Agent Description: BNT163 HSV-2 RNA-lipid nanoparticle (RNA-LNP) vaccine. The strategy behind the BNT163 RNA vaccine candidate is to induce immune responses that block HSV cellular entry, inhibit cell-to-cell spread, and counteract HSV’s inhibitory effects on the complement system and antigen clearance.

The RNA drug substance of BNT163 is 1:1:1 mixture of three highly purified single-stranded, 5'-capped nucleoside-modified RNAs. There are three RNAs in BNT163, each encode one of three HSV-2 glycoprotein ectodomains – C, D, and E (gC2, gD2, gE2). An encoded secretory signal peptide guides translocation of the nascent protein for further processing.

The drug product is a preservative-free, sterile suspension/dispersion for dilution for IM administration and contains

RNA formulated in LNP in aqueous cryoprotectant buffer.

Is a novel vector system, approach or technology used for this clinical trial? NO

Gene transfer agent delivery method: Lipid nanoparticle mRNA vaccine

Intended target: Neutrophils, monocytes, and dendritic cells infiltrating to the site of IM vaccine administration and the draining lymph nodes.

Potential for shedding: No biosafety shedding concerns.

Based on risks observed with SARS-CoV-2 vaccine BNT162b2 (with the same LNP carrier system, the same nucleoside-modified RNA, and the same untranslated elements of the antigen-encoding RNA as in BNT163), the safety profile for BNT162b2 is expected to include local and systemic reactogenicity:

Local reactogenicity with BNT162b include injection site pain (>80%), fatigue (>60%), headache (>50%), myalgia (>40%), chills (>30%), arthralgia (>20%), pyrexia and injection site swelling (>10%), and these adverse reactions were usually mild or moderate in severity and resolved within a few days after vaccination. A similar local and systemic reactogenicity profile is expected in this trial.

Based on post-marketing data, very rare (<1 in 10,000 subjects) cases of myocarditis and pericarditis have been observed in people vaccinated with RNA-based COVID-19 vaccines, particularly within 7 d following the second dose.

The possibility of increased risk of HSV acquisition or worsening of HSV disease post-vaccination has been rarely reported with other viral vaccines (e.g., Dengue, HIV). To date, these risks have not been observed in HSV vaccine trials. However, limited data are currently available to exclude this possible risk occurring after BNT163 vaccination.

Are "Standard Precautions," Biosafety Level 2 (BSL-2) equivalent, practices appropriate for ensuring clinical trials personnel safety? YES

This Registration Meets IBC Criteria for Approval: YES. I recommend approval, as submitted."

- The amendment was discussed by the committee members.
- All members were in favor of approval.
- The HGT registration amendment is approved as submitted.

HGT Administrative Actions: #20

Research Administrative Actions: #57

SECTION III-B. NIH/OBA and IBC Approval Before Initiation

6. Sahingur.....25-220B-1

- Dr. Tucker Piergallini presented the registration. This registration is for the crossing and/or use of transgenic mice. The lab studies periodontal diseases and hypothesizes that deregulated immune responses and senescence related events can contribute to periodontitis. To elucidate the impact of inflammation, senescence, and bacteria axis in aging periodontal tissues and disease phenotype, they will use p21Cre.GFP.ERT2/R26.DTAL/L mouse strain. The mouse strain expresses "Diphtheria toxin A" (DTA) in a subset of cells expressing higher p21, a senescence marker. p21 positive senescent cells will be removed through administration of tamoxifen. These mice will be bred and used in various studies such as oral administration of bacteria, Ligature-induced periodontitis model, and interventions using quercetin, dasatinib and fisetin. DTA is expressed in a subset of cells, does not accumulate, and is not secreted. NIH OSP approval will be requested following IBC approval. Containment has been set to BSL-1 and ABSL-1.
- The registration was discussed by committee members.
- Training was complete.
- All members were in favor of approval.

- The IBC registration was approved.

SECTION III–D. Experiments that Require IBC Approval Before Initiation:

7. Bar.....25-224D-1,3

- Ms. Stephanie Adams-Tzivelekidis presented the registration. This registration is for the generation and/or use of 2nd generation lentiviral vectors overexpressing BREC1 in commonly used cell lines in the HIV field. Human immunodeficiency virus (HIV) contains unique regions within the LTRs that are potentially targetable by bacterial recombinases for therapeutic and cure strategies. The lab has developed a novel simian human immunodeficiency virus (SHIV) construct with loxBTR sites inserted into the SHIV LTRs. This allows the virus to be targeted by the CRE-like recombinase BREC1. These new cell lines will allow the Bar lab to perform in vitro analysis of BREC1 recombination on novel SHIVs with loxBTR sites. Containment has been set to BSL-2.
- The registration was discussed by committee members.
- Training was complete.
- All members were in favor of approval.
- The IBC registration was approved.

8. Bernstein25-254D-1,3 O-1

- Ms. Stephanie Adams-Tzivelekidis presented the registration. This registration is for the generation and/or use of 3rd generation lentiviral vectors and CRISPR elements, which were purchased from addgene, and are used in tissue culture only. This project aims to study the potential impacts of genetic mutations in DNA repair factors observed and cataloged in cancer patients. This work will involve molecular studies focusing on DNA double-strand break repair enzymes such as BLM, PALB2, RECQL4, RAD51, and the family of RAD51 paralogs as well as translesion synthesis genes, base and nucleotide excision repair genes. CRISPR and lentivirus vectors will be used to knockout or knockdown the genes of interest. In addition, lentiviruses will be used to express the genes of interests and related mutants, such as BRCA1 and 2. Containment has been set to BSL-2.
- The registration was discussed by committee members.
- Training was complete.
- All members were in favor of approval.
- The IBC registration was approved.

9. Chen-Plotkin ..25-165D-1,3 O-1

- Ms. Stephanie Adams-Tzivelekidis presented the registration. This registration is for the generation, and/or use of a 3rd generation lentiviral vectors purchased from Addgene. The Lentivirus will be delivering CRISPR components to modify the expression levels of genes associated in the pathogenesis of neurodegenerative diseases (i.e. Parkinson's Disease and Alzheimer's Disease). The lab is packaging lentiviral vectors in HEK293T cells and transduce human inducible pluripotent stem cells (iPSCs) harboring an inducible dCAS9 system to perform CRISPR inhibition and/or activation. The successfully transduce iPSCs are then differentiated

into glutamatergic neurons or microglia for further investigation. Containment has been set to BSL-2.

- The registration was discussed by committee members.
- Training was complete.
- All members were in favor of approval.
- The IBC registration was approved.

10. Chung.....25-221**D-4**

11. Chung.....25-222**D-1,4**

- Ms. Marie-Luise Faber presented the registrations. These registrations are for the generation and/or use of Canine adenoviral vectors and 2nd generation lentiviral vectors. The lab will use a canine adenoviral vector to explore neuronal circuits. The vector will be injected in Cre mice via the axon terminal region to express Cre and Flp recombinase. The vector is made at UC Irvine. A lentiviral vector will deliver *ic⁺⁺*, ChR2 and eYFP to be able to either enhance or suppress neuronal activity under illumination. The vector will be used in Cre mice. The lentiviral vectors are a second-generation vector and come from Salk Institute. This established second gen vector has a high transduction efficiency in neurons. Containment for 25-221 has been set to BSL-1 and ABSL-1, and containment for 25-222 has been set to BSL-2 and ABSL-2.
- The registrations were discussed by committee members. Dr. Daniel Kessler asked for the delivery method to be added to the project description of 25-222.
- Training was complete.
- All members were in favor of approval.
- The IBC registrations, 25-221 and 25-222 were approved, pending update to project description for 25-222.

12. Corder25-029**D-1,4**

13. Corder25-030**D-4**

- Ms. Marie-Luise Faber presented the registrations. These registrations are for the generation and/or use of modified rabies virus and adeno associated viral vectors. The lab will model neural activity within and across the synaptic connections of these brain circuits by using AAVs to express optogenetic ion-channels (light sensitive) or chimeric G-protein Coupled Receptors (also known as Designer Receptors Exclusively Activated by Designer Drugs [DREADDs]) that allow them to turn on or off these neurons to assess their contribution to pain-related behaviors in mice. Transgenic mouse lines will be used in conjunction with modified rabies virus to describe basic anatomical structures of somatosensory pathways. The modified mutant rabies virus is capable of one round of infection but can go no further and overcomes this previous uncertainty of trans-synaptic infection or labeling. This work will help map the neuronal connections in the mouse brain as they relate to the perception of pain. The rabies virus has a deleted G portion and is pseudotyped to EnvA protein on the target cell. Containment for both registrations has been set to BSL-1 and ABSL-1.
- The registrations were discussed by committee members. Dr. Daniel Kessler asked for the delivery method to be added to the project description of 25-030.

- Training was complete.
- All members were in favor of approval.
- The IBC registrations, 25-029 and 25-030 were approved, pending update to project description.

14. Dowling25-191**D-1,3 O-1**

- Ms. Amanda Wong presented the registration. This registration is for the generation and/or use of 3rd generation lentiviral vectors. The lab is investigating if lentiviral expressions of genes that are mutated in neuromuscular disorders (NMD's) can rescue muscle function and lessen disease phenotypes. The lab aims to create various models using 3rd generation lentiviral vectors and CRISPR/Cas 9 by way of blocking the expression of or to overexpress genes involved in muscle function; or targeting the genes of interest to create nonsense, frameshift null, and point mutations that mimic mutations seen in human NMD patients. Lentiviral particles are prepared by transient transfection of 293T cells with expression, packaging, and envelope plasmids, after which virus is collected and purified by filtration and centrifugation. Virus is used to transduce primary cells isolated from mouse or human tissues and/or immortalized cell lines, which are then tested for their functionality in vitro. Containment has been set to BSL-2.
- The registration was discussed by committee members.
- Training was complete.
- All members were in favor of approval.
- The IBC registration was approved.

15. Drapkin25-248**D-4 O-2**

- Mr. Edwin Sui prepared the registration and was presented by Ms. Marie-Luise Faber. This registration is for the generation and/or use of mRNA encapsulated in lipid nanoparticles. The lab is investigating the role of LINE1 ORF1p in ovarian cancer as a potential therapeutic target and biomarker. LINE1 is a transposable element protein consisting of ORF1p and ORF2p that is normally repressed but becomes strongly upregulated in ovarian cancer. ORF1p is absent in benign tissues and there is evidence of its robust expression in several tumor models. The study will test an mRNA-LNP vaccine (developed with Weissman Lab and Acuitas Therapeutics) for its ability immune responses versus ORF1p in mice. Tumor-naive mice will receive varying doses of ORF1p mRNA-LNP followed by assessment of T cell responses. Further experiments will study the effect of the vaccine on tumor growth and survival. The overarching goal is to determine whether an ORF1p mRNA vaccine can promote antitumor immunity and serve as a novel cancer immunotherapy approach. Containment has been listed as BSL-2 and ABSL-2.
- The registration was discussed by committee members. Ms. Marie-Luise Faber pointed out that “yes” should have been selected to the question about foreign gene expression and that work can be conducted at BSL-1 and ABSL-1.
- Training was complete.
- All members were in favor of approval.
- The IBC registration was approved, pending registration and containment updates.

16. Facciabene25-231D-4

- Ms. Stephanie Adams-Tzivelekidis presented the registration. This registration is for the generation and/or use of retroviral vectors with ecotropic envelopes expressing CD19 CAR receptor. The lab is producing CD19-targeted chimeric antigen receptor (CAR) T cells targeting the A20 a murine B cell lymphoma cells. CD19 CAR-T cells have transformed the treatment of patients with relapsed or refractory CD19-positive hematologic malignancies. In this project the lab is investigating the impact of the gut microbiome and the impact of bridging radiotherapy on CD-19 CAR T cells. The produced CD19 CAR T cells are injected intravenously into A20 tumor bearing mice, and the expressed GFP will be used to track the CAR T cells in the animal model. Containment has been set to BSL-1.
- The registration was discussed by committee members. Dr. Daniel Kessler asked for the specific retroviral vector to be listed in the project description.
- Training was complete.
- All members were in favor of approval.
- The IBC registration was approved, pending update to project description.

17. Field22-213D-1, 3

- Dr. Sarah Capasso presented the registration. This registration is for the generation and/or use of a 3rd generation lentiviral vector expressing the CAP2 or CAP1 genes. This allowed the lab to study sudden cardiac death as mutations in CAP1 and CAP2 are responsible for cardiomyopathy. The viral vectors are currently being held in storage only. Containment has been set to BSL-2.
- The registration was discussed by committee members. Dr. Sarah Capasso noted that D-3 should be selected under NIH guidelines. Dr. Daniel Kessler noted that “yes” should be selected for the questions about foreign gene expression.
- Training was complete.
- All members were in favor of approval.
- The IBC registration was approved, pending updates.

18. Haldar25-251D-1,3

- Ms. Amanda Wong presented the registration. This registration is for the generation and/or use of 4th generation lentiviral vectors. The lab aims to use 4th generation lentiviral particles to overexpress RALDH3, an enzyme that catalyzes a key step in retinoic acid production, in murine prostate cancer cell lines to more closely model human prostate cancer. With the goal of in-vivo tumor studies in the future. Containment has been set to BSL-2.
- The registration was discussed by committee members. Dr. Daniel Kessler requested a more descriptive title.
- Training was complete.
- All members were in favor of approval.
- The IBC registration was approved, pending update to title.

19. Ma.....25-233**D-4**

- Dr. Sarah Capasso presented the registration. This registration is for the generation and/or use of AAV vectors to study the organization and function of neural networks in different brain regions. The lab will use AAV to 1) trace pre- or postsynaptic partners of specific cell types; 2) record their neural activity via genetically encoded Ca²⁺ sensors, 3) activate or suppress their activity via optogenetic and/or chemogenetic manipulations, and 4) ablate these neurons in mice. Vectors will be purchased from vendors and/or acquired from other researchers. Containment has been set to BSL-1 and ABSL-1.
- The registration was discussed by committee members.
- Training was complete.
- All members were in favor of approval.
- The IBC registration was approved.

20. Lorenzo25-210**D-4 O-1**

- Ms. Marie-Luise Faber did not present the registration. This registration was removed from the agenda, upon further review the Biosafety Officer determined the registration required additional information.
- The IBC registration was tabled until ready for rereview.

21. Shen25-242**D-1,3 O-1**

- Mr. Edwin Sui prepared the registration and was presented by Ms. Marie-Luise Faber. This registration is for the generation and/or use of 2nd generation lentiviral vectors. This lab investigates the role of enzyme cofactor biosynthesis in human and mouse cell lines by targeting key genes, with a particular focus on riboflavin kinase (Rfk), which is essential for FMN and FAD synthesis and thereby critical for metabolic pathways such as the electron transport chain. Using a CRISPR/Cas9 in a lentiviral vector, the lab will evaluate the impact of Rfk deletion in different cellular contexts. This will allow the lab to explore the contribution of Rfk and associated genes to cellular metabolism. Containment has been set to BSL-2.
- The registration was discussed by committee members. Ms. Marie-Luise Faber stated D-3 will be added under the NIH guideline selection.
- Training was complete.
- All members were in favor of approval.
- The IBC registration was approved pending update to NIH guidelines.

SECTION III–O. Experiments that Require IBC Approval Before Initiation:22. Dowling25-187**E-3 O-1**

- Ms. Stephanie Adams-Tzivelekidis presented the registration. This registration is for the creation of transgenic mice. The Penn Chimeric Mouse Facility will perform microinjection of CRISPR components into C57BL/6 mouse zygotes to introduce nonsense or point mutations in the Nebulin gene. This animal model serves as a model for human genetic mutations in Nebulin which lead to neuromuscular diseases. Subsequently, they will use this model to test gene

therapies that allow for read through nonsense mutations. Containment has been set to BSL-1 and ABSL-1.

- The registration was discussed by committee members. Ms. Dorothy Kaplan asked for grammar to be corrected in project description.
- Training was complete.
- All members were in favor of approval.
- The IBC registration was approved, pending updates to project description.

SECTION III–E. Experiments that Require IBC Notice Simultaneous with Initiation:

23. Mangalmurti ..24-173~~E-1~~, D-4

- Dr. Sarah Capasso presented the registration. This registration is for the generation and/or use of Naked DNA/RNA in the form of mitochondrial DNA as an important damage associated molecular pattern (DAMP). DAMPs are host molecules that are released from cells following cellular stress or tissue injury and activate the immune system via pattern recognition receptors. The lab's goal is to establish mitochondrial RNA as an important DAMP in sepsis and systemic inflammation to eventually develop more effective therapy options. The lab will use a synthetic mitochondrial RNA sequence oligonucleotide purchased from Penn IDT and inject it into mice to see if they develop systemic inflammation and lung injury as a result. Containment has been set to BSL-2 and ABL-1.
- The registration was discussed by committee members. Dr. Sarah Capasso noted that NIH guidelines section assignment will be changed to D-4.
- Training was complete.
- All members were in favor of approval.
- The IBC registration was approved, pending update to NIH guidelines section assignment.

3. New Business:

- (a) No New Business Scheduled.

4. Old Business:

- (a) No New Business Scheduled.

5. End Meeting:

- The Institutional Biosafety Committee was adjourned by Dr. Daniel Kessler at **10:55 AM**.

Our next meeting scheduled for Monday, September 22nd, 2025, will be held on site at the EHRS Office with a Teleconference option, at 10:00 am. A light Brunch will be provided.