

Institutional Biosafety Committee:

Present: Dr. Julian Baptiste, Dr. Jessica Buchanan, Dr. Sara Cherry, Dr. Joseph Fraietta, Dorothy Kaplan, Dr. Daniel Kessler, Dr. Andrew Maksymowych, Dr. Maureen O’Leary, Ms. Jessa Yoos, Ms. Denene Wambach

Absent: Dr. Steven Albelda, Dr. Paul Bates, Dr. David Pegues

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

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

1. IBC Minutes: 10-27-2025

- 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. Aggarwal.....#25-073 C-1

Dr. Charu Aggarwal– NEW HGT Protocol Registration

FULL REVIEW

PROTOCOL TITLE: UPCC 13520 CAN-2409 Plus Prodrug with Standard of Care Immune Checkpoint Inhibitor for Stage III/IV NSCLC Patients (LuTK02). (Protocol V7 dated April 20, 2023; Main ICF dated April 27, 2023.)

IBC #25-073, IRB #844087, IND #15442

- Dr. Daniel Kessler introduced the submission and provided a summary and analysis.
- Dr. Maureen O’Leary provided a summary and analysis.

“Project Overview: This first-in-human (FIH) trial is designed to assess the safety, feasibility, and potential activity of a single intravenous (IV) dose of SynKIR-110 administered to subjects with mesothelin-expressing advanced ovarian cancer, mesothelioma, and cholangiocarcinoma.

As a background Chimeric antigen receptor (CAR) T cell therapies have been successful in hematologic malignancies; however, they have not seen the same success in solid tumors. Traditional CD3ζ-based CARs formed by the joining of a binding domain, costimulatory molecule cytoplasmic domains and the CD3ζ cytoplasmic domain into a single chimeric protein have been shown to exhibit constitutive signaling that can adversely affect CAR T cell function. SynKIR-110 is engineered with a multichainCAR design built upon the natural multichain activating killer immunoglobulin like receptors (Called KIRs), which are an important family of immunologic receptors used by T cells and natural killer (NK) cells. The KIR-based CAR (KIR-CAR)used in SynKIR-110 utilizes the SS1 antibody (Ab)-derived scFv to target mesothelin-expressing tumors. The SS1 scFv was chosen specifically for its well defined clinical safety profile when used in other immunotherapies based upon immunotoxin conjugates or traditional CD3ζ-based CAR T cells.

Mesothelin is a membrane-bound protein expressed on normal mesothelial cells of the pleura, pericardium, and peritoneum, with trace amounts found on the epithelial lining of the ovaries, fallopian tubes, tunica vaginalis and rete testis. Mesothelin is also overexpressed in a broad range of solid tumors, including, but not limited to, ovarian cancer, malignant mesothelioma, cholangiocarcinoma, and pancreatic adenocarcinoma. This high expression of mesothelin in solid tumors with limited expression in normal tissues has rendered mesothelin an important therapeutic target for antigen-specific therapies, including antibody-based drugs, vaccines, and chimeric antigen receptor (CAR) T cell therapies.

Mesothelin expression has been identified in the lung. In the single-cell RNA-seq analysis different types of epithelial and immune cells within the lung (alveolar cells type 1 and 2) and Paneth cells, club cells and glandular and luminal cells showed detectable mesothelin mRNA expression. The role of mesothelin in these cell types

remain unknown. This expression in lung is worth noting, as there have been Grade 5 serious adverse events (SAEs) reported by Tmunity Therapeutics and Atara Biotherapeutics in patients receiving mesothelin- targeting CAR T, although both used different scFv binders and signaling regions than Verismo. The SS1 scFv was chosen for use in SynKIR-110 specifically for its well-defined clinical safety profile as both an scFv-directed immunotoxin and CAR T (SS1-4-1BB-CD3z), in the same patient populations included in the initial clinical trial of SynKIR-110. SynKIR-110 may offer an effective alternative treatment modality for patients afflicted with specific-mesothelin-expressing solid tumors, including ovarian cancer, mesothelioma, and cholangiocarcinoma.

Agent Description: SynKIR-110 is an autologous, genetically engineered T cell product that utilizes a novel signaling mechanism designed to more realistically reflect the natural multichain design of lymphocyte signaling pathways, specifically killer immunoglobulin-like receptors (KIRs), which are an important family of immunologic receptors used by T cells and natural killer (NK) cells. The novel signaling mechanism of SynKIR-110 is derived from its use of the KIR transmembrane and cytoplasmic domain which upon binding target promotes the formation of a complex with DAP12 protein dimers to deliver activating signals to T cells. This first-in-class multichain immunoreceptor design preserves CAR T cell anti-tumor functionality in the solid-tumor microenvironment and improves potency in vivo in mouse models when compared with single-chain CARs

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

Gene transfer agent delivery method: Intravenous infusion of CAR-T product.

Intended target: SynKir-110 is a KIR-based CAR using the SS1 antibody to target mesothelin-expressing solid tumors

Other material to be used in preparation of the agent: N/A

Potential for shedding: None

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. Blumberg#24-029 C-1

Dr. Emily A Blumberg– HGT Protocol Registration Amendment V4

AMENDMENT

PROTOCOL TITLE: CYTOMEGALOVIRUS (CMV) VACCINE IN ORTHOTOPIC LIVER TRANSPLANT

CANDIDATES. (Protocol V4 dated June 16, 2025; All Sites ICF V3.1 dated February 21, 2024; U Penn ICF dated January 25, 2024; COLT Other site ICF V3 dated March 4, 2024.)

IBC #24-029, IRB #855964, IND #029672, PROTOCOL #NCT06075745

- Dr. Daniel Kessler introduced the submission and provided a summary and analysis.
- Dr. Maureen O’Leary provided a summary and analysis.

“Project Overview: CYTOMEGALOVIRUS (CMV) VACCINE IN ORTHOTOPIC LIVER TRANSPLANT CANDIDATES

Cytomegalovirus (CMV) is a common virus that many people have been exposed to and is easily spread by close personal contact. While CMV rarely causes problems in healthy people, CMV can cause life-threatening infection in people with a compromised immune system, such as those who have received a liver transplant (LTx). After becoming infected, the virus remains in the body life-long. The virus can be transmitted from CMV seropositive (infected) persons through organ donation.

The primary hypothesis of this study is that CMV vaccination of seronegative persons will induce protective immunity to CMV and decrease the risk of serious CMV infection and need for antiviral therapy after LTx.

The primary objective of this study is to assess the safety of pre-Transplant Triplex vaccination among Liver Transplant candidates, in conjunction with assessing the effect of pre-Transplant Triplex vaccination on duration of CMV within the first 100 days post-Transplant who will receive pre-emptive therapy as CMV prevention.

Agent Description: CMV-MVA Triplex is an investigational multiple-antigen recombinant Modified Vaccinia Ankara Virus (MVA) based vaccine expressing genes encoding 3 immunodominant Cytomegalovirus (CMV) proteins: UL83 (pp65), UL123 (IE1, exon 4), and UL122 (IE2, exon 5). MVA is an attenuated pox virus that is made avirulent through repeated passages of the parent virus, vaccinia virus Ankara [1]. The MVA was modified to incorporate CMV genes [2]. The investigational vaccine has been evaluated in Phase 1 and 2 clinical trials, including healthy adults and immunocompromised recipients of allogeneic (allo) and autologous (auto) hematopoietic stem cell transplant (HCT).

MVA is attractive as a therapeutic agent due to its previous safety record as a smallpox vaccine in the young and elderly. Recently published data from a randomized, placebo-controlled, double-blind study has shown that MVA

was safe, well tolerated and immunogenic when used as a vaccine in HCT recipients.

Amendment: Changes in this amendment are mostly administrative.

More sites activated now 18 sites

Vaccination for first living donor liver transplant subject

Vaccine will be administered 14-days before the liver transplant

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

Gene transfer agent delivery method: Injection of product.

Intended target: The therapeutic transfer of recombinant DNA to a human host in this study is not classified as 'gene therapy' by the NIH Recombinant DNA Committee as MVA does not integrate into host cell DNA [26]. The intended target cells include resident dendritic cells, monocytes and macrophages. The MVA DNA will remain within the cytoplasm of these antigen presenting cells, which will process and present the epitopes encoded by the CMV transgenes. Since there is no evidence that MVA crosses the nuclear membrane, it will remain in the cytoplasm of susceptible cells and degrade in a defined time period. However, persistence of expression is sufficient to generate an immune response expressed by the MVA vector.

Other material to be used in preparation of the agent: Manufacturing

Potential for shedding: None

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. Frey.....#25-329..... C-1

Dr. Noelle Frey– NEW HGT Protocol Registration **FULL REVIEW**

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial of Descartes-08 in Patients With Generalized Myasthenia Gravis (MG) (Protocol V1.1 dated December 6, 2024; Main ICF dated December 3, 2024.)

- Dr. Daniel Kessler introduced the submission and provided a summary and analysis.
- Dr. David Pegues provided a summary and analysis. Dr. Pegues’ submission was read into record by Dr. Maksymowych.

“Project Overview: Autoimmune myasthenia gravis (MG) is a disorder of neuromuscular transmission caused by pathogenic autoantibodies that target critical components of the nicotinic acetylcholine receptor or other proteins supporting the receptor’s function. Current treatment strategies typically utilize drugs including prednisone, azathioprine and mycophenolate mofetil, among others. Patients treated with these medications often have unacceptable side-effects, benefit only from very high doses, and become dependent on repeated rescue therapies such as IVIG or plasma exchange, requiring frequent hospitalizations. Thus, MG therapies with better efficacy and tolerability are needed.

Descartes-08 is an autologous CAR T directed against B-cell maturation antigen (BCMA) a cell surface glycoprotein and non-tyrosine kinase receptor that is being developed for treatment of multiple myeloma and autoantibody associated autoimmune diseases, including generalized myasthenia gravis (gMG) and systemic lupus erythematosus (SLE).

Primary objective: To evaluate the efficacy of Descartes-08 as assessed by the proportion of Myasthenia Gravis Activities of Daily Living (MG-ADL) responders at Month 4.

Secondary objectives:

- To evaluate the efficacy of Descartes-08 vs. placebo assessed by the proportion of responders using the Myasthenia Gravis Composite (MGC) and Quantitative Myasthenia Gravis (QMG) scores at month 4.
- and by comparing the mean decrease from baseline at Month 4 using the MG-ADL, MGC and
- QMG scoring systems.
- To evaluate the safety, tolerability and efficacy of Descartes-08 versus placebo.

Individual participant duration lasts approximately 14 months, as follows:

Part 1:

- Pre-infusion portion of approximately 2 months, during which patients with gMG will be screened, undergo leukapheresis, and randomized to receive Descartes-08 or placebo.

- Infusion portion of approximately 1.5 months, during which subjects will receive 6 once-weekly intravenous infusions of Descartes-08 or placebo.
- Follow-up portion of 2.5 months, during which participants will undergo monthly evaluations with primary endpoint evaluation at Month 4 (2.5 months after the last infusion).

Part 2:

- Open-label extension portion of approximately 8 months, during which participants may receive six once-weekly intravenous infusions of Descartes-08 open-label (cross-over infusions if randomized to placebo, retreatment infusions if randomized to Descartes-08).

Agent Description: Descartes-08 is an autologous CAR T-cell product that uses mRNA transfection to create T-cells that only transiently express a CAR directed against BCMA that aims to limit uncontrolled expansion and proliferation of circulating CAR T-cells and concomitant toxicities such as CRS and neurotoxicity. The scFv portion of this CAR was derived from a mouse anti-human-BCMA monoclonal antibody. The construct also contains the hinge and transmembrane regions of the CD8-alpha molecule, the signaling moiety of CD28, and the signaling domains of CD3-zeta.

Descartes-08 is provided in the frozen state in single-use vials each containing a premeasured number of cells between 400 to 2000 x 10⁶ viable CAR+ cells.

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

Gene transfer agent delivery method: I Rather than using viral transduction for T cell gene transfer, the Descartes-08 CAR uses mRNA transfection to create a transiently modified T-cell product. mRNA is taken up into the cytoplasm of the T cell, expressed transiently, and degraded. The CAR BCMA protein that is expressed on the surface of the cell is also reduced over days, either by protein turnover or halved with each round of T-cell division.

Intended target: Plasma cells that normally express BCMA with the aim of reducing production of auto-antibodies targeting the nicotinic acetylcholine receptor.

Other material to be used in preparation of the agent: Manufacturing

Preclinical studies: As of August 25, 2024, Descartes-08 has been administered to 67 participants with gMG. The most common toxicity was infusion-related reaction manifesting as fever, chills, myalgia, arthralgia, nausea, headache and fatigue. There have been no instances of CRS or ICANS requiring administration of tocilizumab or steroids reported.

While initial decreases from baseline in all MG disease scores were observed for both Descartes-08 and placebo-treated patients at Month 1, these decreases were maintained in the Descartes-08 group up to Month 3, whereas MG disease scores trended towards baseline for the placebo group.

Potential for shedding: N/A

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. Safety profile of the mRNA transfected CAR T cell expressing BCMA appears to be well tolerated without SAEs, and I recommend approval of the protocol.

- 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.

IBC #25-329, IRB #859614, IND #18964, Protocol # RNAC-MG-002 (AURORA)**4. Irwin#24-135.....C-1**

Dr. David Irwin– HGT Protocol Registration Amendment V8 **AMENDMENT**

PROTOCOL TITLE: 0BA Phase 1b Open-Label, Multicenter, Dose Escalation Study To Assess the Safety, Tolerability, and Pharmacodynamic Effects Of A Single Dose of PBFT02 Delivered Into The Cisterna Magna (ICM) Of Adult Participants With Frontotemporal Dementia (FTD) And Mutations In The Granulin Precursor (GRN) Or Chromosome 9 Open Reading Frame 72 (C9orf72) Genes. (Protocol V8 Amendment G dated July 1, 2025; Main ICF V8 dated August 12, 2025; SPICF V7 dated August 12, 2025.)

IBC #24-135, IRB #848900, IND #26814, Protocol #PBFT02-001

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

“Project Overview: Frontotemporal lobar degeneration (FTLD) is the second leading cause of adult-onset neurodegeneration in patients under 60 years of age. It manifests as a spectrum of clinical syndromes, one of which is frontotemporal dementia (FTD). FTD is a progressive and uniformly fatal disease, with death typically occurring within 10 years of clinical presentation. This study is investigating if a single ICM dose of PBFT02 will be safe, well tolerated, and increase cerebrospinal fluid (CSF) progranulin (PGRN) levels in participants aged > 35 and < 75 years with symptomatic Frontotemporal Dementia (FTD) and mutations in the granulin Precursor (GRN)

or Chromosome 9 Open Reading Frame 72 (C9orf72) Genes. It will also investigate if elevation of CSF PGRN levels in such participants will slow FTD-related neurodegeneration and clinical disease progression, including signs and/or symptoms of amyotrophic lateral sclerosis (ALS) in the FTD-C9orf72 participants.

This is an amendment to incorporate additional monitoring and implementation of low-dose prophylaxis to mitigate risk of VTE in response to the serious adverse event of pulmonary thromboembolism that occurred in 1 participant. Updates were also made to laboratory assessments and eligibility criteria to screen for and exclude participants with inherited thrombophilias and acquired hypercoagulable states. Changes were also made to exclude participants with advanced FTD, as these individuals are increasingly unable to complete the required study assessments and provide longitudinal data. Optical coherence tomography will no longer be collected, since most study participants are unable to comply with the assessment longitudinally.

Finally, for clarity, the study objectives and endpoints, eligibility criteria, the Schedule of Events, and the Schedule of Individual Biomarker Assessments were updated to reflect planned assessments and analyses.

Agent Description: PBFT02 (AAV1.CB7.CI.hPGRN.rBG) is an AAV vector-based gene therapy.

Gene insert: Codon-optimized version of the human granulin precursor (hGRN) gene encoding progranulin (PGRN).

Control element: regulatory element derived from the chicken beta-actin (CBA) promoter Human cytomegalovirus immediate-early enhancer (CMV IE).

Other elements: CBA intron consisting of a CBA splice donor and a rabbit beta-globin (rBG) splice acceptor element; polyadenylation (PolyA) signal derived from the rBG gene; and two inverted terminal repeat sequences (ITRs).

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

Gene transfer agent delivery method: Single dose (either 4.5x10¹³ genome copies or 2.2x10¹³ genome copies) administered via CT-guided sub-occipital administration into the cisterna magna (ICM).

Intended target: PBFT02 is intended to deliver a functional copy of the GRN gene to the brain. ICM administration was chosen because studies have shown that ICM administration of vector achieves more efficient vector distribution than administration via lumbar puncture and appears to carry less risk of immunity to the transgene than intracerebroventricular administration.

Other material to be used in preparation of the agent: PBFT02 is supplied frozen as a sterile solution in intrathecal final formulation buffer diluent (ITFFBD), which is composed of 1 mM sodium phosphate, 150 mM sodium chloride, 3 mM potassium chloride, 1.4 mM calcium chloride, 0.8 mM magnesium chloride, and 0.001% poloxamer 188, pH 7.4.

Potential for shedding: Shedding risk typical of AAV vectors. Vector absent from saliva and feces 30-37 days after dosing in the first 8 participants. Normal precautions in place.

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.

5. Porter.....#25-003 C-1

Dr. David L Porter- HGT Protocol Registration Amendment V10 **AMENDMENT**
PROTOCOL TITLE: A phase 1/2, open-label, safety and dosing study of autologous CART cells (desmoglein 3 chimeric autoantibody receptor T cells [DSG3-CAART] or CD19-specific Chimeric Antigen Receptor T cells [CABA-201]) in subjects with active, pemphigus vulgaris. (Protocol V10 dated September 30, 2025; Sub Study ICF dated October 29, 2025.)

IBC #25-003, IRB #842584, IND #19217, Protocol #CAB-101

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

“Project Overview: Pemphigus vulgaris (PV) is a rare, life-threatening autoimmune blistering disease caused by autoantibodies to skin cell adhesion proteins known as desmogleins (DSGs). PV is associated with considerable morbidity and mortality. Left untreated, PV is frequently fatal. Mortality has decreased to 1.6% to 12% since the introduction of corticosteroids and adjuvant immunosuppressants, but remains approximately 2- to 3-fold higher in patients with pemphigus than in the general population. Autoimmune B cells in PV express an anti-DSG3 B cell receptor (BCR), a surface-bound autoantibody identical in specificity to the antibody that the B cell will secrete once activated to mature antibody-secreting cell. Thus, the anti-DSG3 BCR uniquely marks the pathogenic autoimmune B cell population in PV. After CD20-targeted B cell depletion with rituximab, serum anti-DSG3

antibody titers fall to the normal range in PV patients, indicating that short-lived plasma cells produce most if not all of the autoantibodies in PV, and hence direct targeting of CD20+ memory B cell precursors indirectly depletes autoantibody-secreting. Started with DSG3 CART, but now moving to pan-B cell depletion with CD19 CAR.

The research is being done to determine the maximum dose of an investigational drug called autologous desmoglein 3 chimeric autoantibody receptor T cells (DSG3-CAART) that can be safely given to patients with pemphigus vulgaris to target and kill only the B cells that are making the autoantibodies that attack DSG3 or a substudy that is now the focus in using CD19 CART. The rationale for this sub-study is to explore if CABA-201, a CAR T with a different construct in the targeting domain from desmoglein 3 chimeric autoantibody receptor T cells (DSG3-CAART), can demonstrate improved clinical and antibody response while maintaining a favorable safety profile in patients with PV. A major question is if CD19 CAR is effective and what preconditioning regimen if any is needed.

Agent Description: The investigational medicinal product (IMP), CABA-201, is a fully human CD19-targeting CAR containing the 4-1BB intracellular costimulatory domain. The structure and functional design of CABA-201 is similar to the FDA approved CAR T cell therapy, tisagenlecleucel, thus, similar performance is expected.

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

Gene transfer agent delivery method: Intravenous infusion of CAR-T product.

Intended target: Pemphigus vulgaris (PV) disease. Immune system cells.

Other material to be used in preparation of the agent: The starting materials for manufacturing of CABA-201 are the patient's leukapheresis product and the lentiviral vector encoding the CABA19-IC78 CAR protein.

Potential for shedding: N/A

Amendment: Changes include: Clarified documents including prior and concomitant therapies and mitigation strategies.

Added rationale for current sub-study to assess whether preconditioning is required for CART expansion and durability. Assess safety and efficacy of different preconditioning therapies. Clarified patient number for preconditioning cohort. And revised dose escalation plan. And how this will be assessed for selection criteria. Clarified retreatment schedule and selection. Updated oversight information. Updated benefit/risk assessment. Aligned HUP with other studies using agent. Very extensive update to clarify guidelines. Updated schedule of activities to align with standard of care.

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.

6. Svoboda.....#23-110..... C-1

Dr. Jakub Svoboda– HGT Protocol Registration Amendment V5 **AMENDMENT**

PROTOCOL TITLE: Phase I Trial of TmCD19-IL18 CAR T Cells in Patients with Relapsed or Refractory CD19+ Cancers. (Protocol V5 dated October 13, 2025; Main ICF V7 dated October 13, 2025; Retreatments ICF V4 dated October 13, 2025.)

IBC #23-110, IRB #853970, IND #29676, SPONSOR #12423

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

"Project Overview: The project evaluates safety, tolerability, manufacturing feasibility, pharmacokinetics/bioactivity, and preliminary anti-tumor activity of TmCD19-IL18 CAR T cells in adults (≥18) with relapsed/refractory CD19+ cancers, initially focusing on Non-Hodgkin lymphoma. Objectives include defining a maximum tolerated dose (MTD) and a feasible dose for potential expansion, characterizing CAR T-cell expansion and persistence, B-cell depletion, and early efficacy measures such as ORR, DOR, PFS and OS by cohort. Long-term follow-up to 15 years is designed to detect delayed toxicities, insertional oncogenesis, and persistence of genetically modified T cells after an integrating lentiviral vector product.

Amendment: TmCD19-IL18 CAR T cells, Protocol Version 5.10 Amendment (10-13-2025). Phase I, single-center, open-label, dose-finding and cohort-specific expansion study of intravenous (IV) TmCD19-IL18 CAR T cells in adults with relapsed or refractory CD19+ malignancies (initially Cohort A: NHL). Up to 24 DLT-evaluable subjects (up to 40 undergoing apheresis) receive a single IV infusion at one of up to five dose levels (DL-1 to DL3) following lymphodepleting chemotherapy; dose escalation uses a 3+3 design with DSMB oversight and protocol-defined DLT review. Subjects are followed for up to 15 years post-infusion per FDA

gene-therapy guidance. This Version 5 amendment formalizes opening of a Retreatment Phase (approved July 2025) for clinically benefiting subjects, adds detailed retreatment eligibility, dosing and follow-up schedules (Appendices 3-4), and updates long-term follow-up language and current huCART19-IL18 experience.

Agent Description: Source/Vector System: Autologous T cells collected by apheresis and lentivirally transduced ex vivo at the Penn CVPF to generate TmCD19-IL18 CAR T cells. The final drug product is a cryopreserved cell suspension in infusion bags for IV administration.

Construct/Modifications: The lentiviral vector encodes a CD19-directed chimeric antigen receptor (human anti-CD19 scFv) fused to human T-cell signaling/costimulatory domains, plus human interleukin-18 (IL-18) expressed from the same transcript via a viral 2A self-cleaving sequence (Thosea asigna virus T2A). The vector is a self-inactivating (SIN) lentiviral system consistent with Penn's existing CAR T platform; integration into host T-cell genomes is required for durable CAR/IL-18 expression.

Transgene/Cargo: Human anti-CD19 CAR (humanized scFv with human intracellular 4-1BB/CD3ζ-like domains, per Penn platform) plus human IL-18, enabling CD19-specific T-cell activation alongside constitutive IL-18 secretion intended to enhance Th1 polarization, proliferation, and anti-tumor activity.

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

While the lentiviral backbone is an established platform, co-expression of IL-18 in a CD19 CAR T product is an enhanced/novel immunostimulatory approach (building on emerging huCART19-IL18 experience but not yet standard of care).

Gene transfer agent delivery method: Single IV infusion of TmCD19-IL18 CAR T cells on Day 0 after a standard lymphodepleting chemotherapy regimen (e.g., fludarabine/cyclophosphamide or other physician-chosen regimen; LD is not considered investigational in this study). Dose is based on transduced cells; Cohort A evaluates up to five dose levels: DL-1 (2×10^6), DL1a (5×10^6 , added in Amendment V4), DL1 (7×10^6), DL2 (2×10^7), and DL3 (6×10^7 TmCD19-IL18 cells), each given as a single IV infusion by gravity or slow IV push at 10–20 mL/min. Staggering rules for initial infusions within dose levels are specified in Section 3.2 to support DLT evaluation.

Intended target: *Ex vivo* lentiviral transduction of autologous T cells; in vivo target is CD19 expressed on malignant B cells in NHL and other CD19+ B-cell malignancies. The protocol describes robust CAR expression using Penn's existing CART19 platform; exact clinical-grade transduction efficiency is lot-dependent but is expected to be consistent with prior CART19/huCART19 products and sufficient to achieve defined cell-dose targets for infusion.

Other material to be used in preparation of the agent: Onsite handling is limited to the cryopreserved cell product shipped from CVPF and stored/handled per the TmCD19-IL18 IP Handling Manual (cryoprotectant components are similar to other Penn CAR T products; detailed composition in pharmacy/IP documents). No helper virus or packaging cell line is present at the bedside; all vector production and release testing occur upstream at manufacturing. Lymphodepleting chemotherapy regimens are standard, commercially available agents (e.g., fludarabine and cyclophosphamide) prepared through institutional pharmacy.

Preclinical Studies: The protocol summarizes in vitro CD19-specific cytotoxicity and cytokine secretion data for IL-18-secreting CAR T cells, plus in vivo xenograft models in which CD19 CAR-IL-18 products show enhanced expansion, Th1 skewing, and improved tumor control compared with conventional CART19, without clear evidence of uncontrolled proliferation in animal models. The "Current Clinical Experience" section also cites ongoing huCART19-IL18 clinical data (NHL, CLL, ALL cohorts) demonstrating high response rates with manageable rates of grade ≥ 3 CRS/neurologic events, providing a safety/efficacy rationale for proceeding with TmCD19-IL18.

Potential for shedding: No replication-competent lentivirus (RCL) is intended to be present in the final product; patients receive ex vivo-modified autologous T cells. Thus, "shedding" risk primarily relates to long-lived CAR T cells and the very low probability of emergent RCL from integrated vector sequences. The protocol includes RCL considerations in toxicity management and specifies that VSV-G RCL testing will not be performed routinely; instead, blood samples are banked for future RCL testing if indicated. Quantitative PCR is used to monitor TmCD19-IL18 persistence, and testing continues until two sequential negative assays document loss of CAR T cells. Long-term follow-up for up to 15 years (initial and retreatment) is consistent with FDA guidance for integrating gene therapy products.

From a biosafety standpoint, staff exposure risks mirror other autologous CAR T products: handling cryobags/tubing, managing blood and body fluids during apheresis, infusion, and post-infusion care, and handling clinical specimens routed to TCSL. Standard BSL-2 practices and bloodborne-pathogen precautions as described in NIH Guidelines and CDC BMBL are appropriate for minimizing occupational risk.

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. Overall, the amendment tightens operational detail and long-term surveillance without introducing new biosafety hazards for personnel, subjects, or the community. This reviewer recommends approval of the amendment as submitted. 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.

7. Tanyi.....#22-284..... C-1

Dr. Janos L Tanyi- HGT Protocol Registration Amendment V [4,5]6.....**AMENDMENT**

PROTOCOL TITLE: A Phase 1 Study of SynKIR-110, Autologous T cells Transduced with Mesothelin KIR-CAR, in Subjects with Mesothelin-Expressing Advanced Ovarian Cancer, Cholangiocarcinoma, or Mesothelioma. (Protocol V4 dated June 6, 2024; Protocol V5 dated October 28, 2024; Protocol V6 dated March 11, 2025; Penn ICF dated October 11, 2022; Pre Screening ICF dated October 28, 2022; Out of Specification ICF dated November 30, 2023.)

IBC #22-284, IRB #852470, IND #28693, PROTOCOL #STAR-101

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

“Project Overview: Project Overview: This is a Phase 1, FIH, multicenter, open-label, dose-escalation pilot study of a single IV gravity drip infusion of SynKIR-110 (autologous T cells expressing a mesothelin-binding motif on a KIR with DAP12 cell activation dimer protein) in subjects with advanced, mesothelin-expressing tumors (ovarian cancer, primary peritoneal cancer, fallopian tube cancer, cholangiocarcinoma, or mesothelioma). Up to 42 subjects will be assessed to determine the safety and feasibility of treatment with SynKIR-110. Informed consent will be obtained from subjects prior to participation in this study.

The study includes an enrollment screening period (pre-leukapheresis safety/eligibility and leukapheresis visits), treatment period (administration of non-myeloablative lymphodepleting chemotherapy followed by a single infusion of investigational product), a 12-month follow-up period or until disease progression, and a 15 year long-term safety follow-up study.

Up to 6 cohorts of 3 to 6 subjects per cohort (dosage range 1 x 10⁷ to 3 x 10⁹ viable transduced cells) will be assessed to determine the safety and feasibility of treatment with SynKIR-110. Doses will be escalated following a standard 3 + 3 design until either an MTD or MFD is reached. Additional subjects may be treated to inform the MTD/MFD at the Sponsor’s discretion. A minimum of 6 additional subjects will be treated at the proposed MTD/MFD to further assess safety and potential activity of SynKIR-110.

Amendments 4, 5 and 6: Significant revisions include elimination of mesothelin testing, change of 28 days waiting period to a stagger for subjects 1 and 2, DSMB review required if DLT for 2 or more subjects, and additional subjects are allowed for dose escalation phase for further safety evaluation. No impact of safety profile.

Agent Description: SynKIR-110: autologous T cells transduced with lentivirus to express a mesothelin-binding motif on a KIR with DAP12 cell activation dimer protein. SynKIR-110 utilizes a novel signaling mechanism designed to more realistically reflect the natural multichain design of lymphocyte signaling pathways, specifically killer immunoglobulin-like receptors, which are an important family of immunologic receptors used by T cells and natural killer cells. The novel signaling mechanism of SynKIR-110 is derived from its use of the KIR transmembrane and cytoplasmic domain which upon binding target promotes the formation of a complex with DAP12 protein dimers to deliver activating signals to T cells. This first-in-class multichain immunoreceptor design preserves CAR T cell anti-tumor functionality in the solid-tumor microenvironment and improves potency in vivo in mouse models when compared with single-chain CAR designs that use the CD3ζ and either 4-1BB or CD28 costimulatory domains.

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

Gene transfer agent delivery method: Single IV gravity drip infusion of SynKIR-110.

Intended target: Mesothelin-expressing tumor cells (ovarian cancer, primary peritoneal cancer, fallopian tube cancer, cholangiocarcinoma, or mesothelioma) in vivo.

Other material to be used in preparation of the agent: Manufacturing and Formulation: SynKIR-110 is manufactured using standard CAR-T methods. CD4+ and CD8+ T-lymphocytes are collected from subject leukapheresis material. Following isolation and activation cell culture is initiated and cells are transduced with LVV to express the mesothelin-binding motif on a KIR with DAP12 cell activation dimer protein and expanded for 4 days. The cells are then washed and concentrated to make SynKIR-110, which is a cryopreserved liquid cell suspension intended for intravenous infusion.

Potential for shedding: N/A

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.

8. Tebas#25-356..... C-1

Dr. Pablo Tebas- NEW HGT Protocol Registration **FULL REVIEW**

PROTOCOL TITLE: A Phase I/IIa Randomized, Placebo-Controlled Trial of Conserved-Mosaic T-cell Vaccine in a Regimen with Vesatolimod and Broadly Neutralizing Antibodies in Adults Initiated on Suppressive Antiretroviral Therapy during Acute HIV-1 (Protocol V3 dated September 6, 2024; Main ICF dated April 14, 2025; ICF dated September 18, 2024.)

IBC #25-356, IRB #853217, IND #163770

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

“Project Overview: Protocol A5374 will be conducted at US and non-US clinical research sites (CRSs) with eligible participant population and capacity to perform the study interventions.

Protocol A5374 is a phase I/IIa randomized, two-arm, double-blind placebo-controlled, multi-step strategy trial to evaluate safety and efficacy of therapeutic vaccination with chimpanzee adenovirus (ChAdV)- and poxvirus modified vaccinia Ankara (MVA)-vectored vaccines in a sequential regimen with the Toll-like Receptor 7 (TLR7) agonist vesatolimod (VES) and two broadly neutralizing antibodies (bNAbs) in individuals with HIV-1 who started suppressive antiretroviral therapy (ART) during acute HIV-1. The study consists of four steps including an analytical treatment interruption (ATI).

Step 1: Study Intervention and ART

Step 2: Analytic Treatment Interruption

Step 3: ART Restart

Step 4: Continuation of ATI

DURATION Up to approximately 110 weeks. The total time on study for each participant is dependent on the time spent in the treatment interruption step (Step 2).

SAMPLE SIZE 45 total participants: Arm A: 30 participants, Arm B: 15 participants

POPULATION Individuals living with HIV-1 who initiated ART during acute infection and have maintained viral suppression since ART initiation and for at least 1 year prior to Step 1 entry.

Hypothesis: Administration of therapeutic vaccination using the chimpanzee adenovirus (ChAdV) and modified vaccinia Ankara (MVA)-vectored vaccines in a prime boost regimen delivering highly conserved mosaic HIV-1 immunogens collectively called HIVconsvX in a sequential regimen with the broadly neutralizing antibodies (bNAbs), GS-5423 and GS-2872, and the Toll-like Receptor 7 (TLR7) agonist vesatolimod (VES) to individuals with HIV-1 on effective antiretroviral therapy (ART) initiated during acute HIV-1 infection will be safe and well tolerated. The triple active therapy of vaccine, bNAbs, and TLR7 agonist will result in greater viral control following analytic treatment interruption (ATI) compared to placebo.

Agent Description: (A) ChAdOx1.tHIVconsv1

A 2nd-generation investigational HIV-1 T-cell vaccine: Non-replicating simian (chimpanzee) adenovirus vector ChAdOx1 expressing 6 highly conserved regions of the HIV-1 proteome as one chimeric protein.

NOTE: The ChAdOx1 nCoV-19 vaccine received approval to be supplied in the UK from the Medicines and Healthcare products Regulatory Agency (MHRA) on 30 Dec 2020 and more than 23 million doses have been administered across the UK by the end of Apr 2021. 350 million doses have been given to an estimated 250 million people globally. Poxvirus-vectored MVA.tHIVconsv3 and MVA.tHIVconsv4 entered clinical evaluation in the US in 2019.

(B) Generic Name: Teropavimab. Gilead Product No.: GS-5423

Teropavimab is a recombinant, fully human mAb of the IgG1k isotype that targets the CD4 binding site of HIV-1 gp120.

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

Gene transfer agent delivery method: Active vaccine or placebo will be administered IM into the deltoid muscle, using standard IM injection technique.

At Week 0 and Week 4 when two injections are to be administered, one IM injection should be given in the deltoid muscle of each arm. The C1 vaccine at Week 0 and the M3 vaccine at Week 4 should be administered in the same arm. Likewise, the C62 vaccine at Week 0 and the M4 vaccines at Week 4 and Week 60 should be administered in the same arm.

Intended target: Acute HIV-1 infection (HIV-1 virus)

Other material to be used in preparation of the agent: N/A

Potential for shedding: No concerns for shedding demonstrated in clinical setting with analogous construct used for SARS-CoV-2 (COVID-19) vaccination.

Poxvirus-vectored MVA.tHIVconsv3 and MVA.tHIVconsv4 entered US clinical evaluation in 2019.

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.

HGT Administrative Actions: #14

Research Administrative Actions: #48

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

9. Chung.....25-347B-1 D-4

- This registration was presented by Ms. Stephanie Adams-Tzivelekidi. This registration is for the generations and/ or use of crossing transgenic animals expressing conditionally DTA (Diphtheria Toxin A). When these ROSA-DTA mice are crossed with a Cre recombinase strain, the floxed-STOP cassette is deleted and the Gt(ROSA)26Sor promoter drives expression of diphtheria toxin A in the cre-expressing cells. These ROSA-DTA mice allow selective ablation in a tissue/cell specific manner. The lab is using this tool to achieve targeted in vivo neuronal ablation as a means of suppressing specific neural activity. This will further their understanding into core mechanisms of sleep-wake regulation to develop effective therapeutic strategies for associated psychiatric disorders. 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:

10. Atherton22-287D-1,4

11. Atherton25-312D-4

- These registrations were presented by Ms. Marie-Luise Faber. Registration 22-287 is for the generation and/or use of retroviral vectors with an amphotropic envelope in canines and mice. Registration 25-312 is for the generation and/or use of lipid nano particles mRNA in canines. The lab is developing novel adoptive cellular therapies for human patients utilizing a comparative oncology approach in which cellular therapies. For 22-287 no more than 15 client owned dogs will be used to collect data on these therapies to support early phase human trials. The lab will start clinical testing in dogs and with autologous CAR T trial of canine oncology patients diagnosed with histiocytic sarcoma. They will treat no more than 15 dogs with intravenously administered anti-STEAP1 CAR T cells following intravenous bendamustine preconditioning. The first 5 dogs will receive a single dose of autologous anti-STEAP1 CAR T cells as mono therapy and 10 subsequent dogs will receive anti-STEAP1 CAR T cells followed by 5 doses of lipid encapsulated nanoparticles containing STEAP1 mRNA (IBC number: 25-312) starting two weeks after CAR T infusion and every 2 weeks thereafter. STEAP1 CAR T cells and STEAP1 vaccines will be administered by either Dr. Matt Atherton or Dr. Jenny Lenz both of whom are

board-certified medical oncologists with experience in conducting research in immune therapies and performing clinical veterinary trials in the oncology clinic. For registration 25-312 mRNA LNP therapies will be developed and tested in vitro and subsequently tested in vivo in small pilot trials of client-owned dogs with naturally occurring cancers. Trials will be limited to 15 dogs or less with the aim of establishing pet dogs as a powerful translational platform that will generate data to directly inform early phase human clinical trial design. STEAP1 mRNA encapsulated in LNPs will be developed in the lab and used in combination with anti-STEAP1 canine CAR T cells for treatment of solid tumors. The canine STEAP1 mRNA LNP vaccines are meant to boost anti-STEAP1 CAR-T cells as a new treatment approach for solid tumors. Containment for 22-287 has been set to BSL-2, ABSL-1, and ABSL-2. Containment for 25-312 has been set to BSL-1, BSL-2, and ABSL-1.

- The registrations were discussed by committee members. Dr. Sarah Capsso noted concern with using Retrovirus with amphotropic envelopes at ABSL-1. Ms. Marie- Luise Faber noted that RCR testing cannot be done on the canine subjects as canine cells degrade too quickly for the process and use. Dr. Daniel Kessler asked if using banked cells would be possible to generate data for RCR testing. Dr. Tucker Piergallini asked why the lab isn't using research animals. Dr. Sarah Capsso recommended collaboration with Dr. Nicola Mason on using client canine and banked cells. Dr Daniel Kessler confirmed that until data from RCR testing is provided and containment levels are confirmed the registration will be tabled.
- Training was complete.
- All members were in favor of approval for registration 25-312.
- The IBC registration 25-312 was approved. Registration 22-287 was tabled until sufficient data and updated safety protocols are provided.

12. Beers25-336D-4

- This registration was prepared by Mr. Edwin Siu and presented by Ms. Amanda Wong. This registration is for the generation and/ or use of adeno associated viral vectors. The lab with an inducible model of pulmonary fibrosis in transgenic mice that carries a mutant form of surfactant protein C (Sftpc). Upon tamoxifen induction in this mouse model, expression of the mutant Sftpc causes lung injury and fibrosis within four weeks. Characterization of this model has identified the activation of the AMP-activated protein kinase (AMPK) pathway as a potential avenue to attenuate the injury and promote normal wound healing. To explore the feasibility of this as a gene therapy target, the lab will use an AAV vector to deliver active gamma AMPK subunit, administered by tail vein injection to the mouse model. This treatment aims to activate the AMPK pathway and thereby reduce lung injury in the mice. A concurrent reporter construct, delivered in a similar AAV strategy, will enable monitoring of lung function and repair. 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.

13. Betley25-346D-1,4

- This registration was prepared by Mr. Edwin Siu and presented by Ms. Amanda Wong. This registration is for the generation and/or use of pseudotyped rabies virus. The lab uses advanced

genetic tools in rodents to selectively manipulate hypothalamic neurons and map their circuits. The hypothalamus, a critical brain region, regulates survival behaviors via neurons that control food seeking, consumption, and fear responses. The lab studies the role of these neurons by analyzing mouse behavior, brain connectivity, and activity under hunger, satiety, and predator fear. This work aims to understand the neural basis of motivation and has implications for treating obesity, anorexia, anxiety, and pain disorders. This tracing of neural connections will be done in a modified mouse model using an EnvA-pseudotyped rabies virus to express GFP & tdTomato in the target tissue. This virus is intracranially injected and is limited to infecting cell types expressing a transgenic receptor, TVA, otherwise the virus is incapable of infecting mammalian cells. Containment was 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.

14. Brenner25-337D-4

- This registration was presented by Ms. Amanda Wong. This registration is for the generation and/or use of adeno associated viral vectors. The lab plans to characterize expression from purchased, replication-deficient rAAVs encoding reporter genes (e.g., firefly luciferase, GFP, mCherry) and comparing this to their previously developed DNA-LNP system. These studies will focus strictly on reporter expression to evaluate relative efficiency, magnitude, duration, and tissue distribution. In vivo studies will involve administration of rAAV to mice (e.g., intravenous, intraperitoneal, or organ-targeted delivery), followed by analysis of transgene expression via luminescence imaging, histology, and molecular assays. In vitro studies will include transduction of relevant cell types for controlled comparison of expression kinetics and efficiency. All vectors will be obtained from commercial vendors; no AAV production, packaging, or helper virus use will occur in the laboratory. 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.

15. Cheng25-338D-4

- This registration was presented by Ms. Stephanie Adams-Tzivelekidi. This registration is for the generation and/or use of mRNA or plasmid DNA (pDNA) to express therapeutic proteins for targeted treatment applications. The lab is developing nanomedicine-based therapies for osteoarthritis and lower back pain. One approach involves using lipid nanoparticles (LNPs) to deliver mRNA or DNA into mouse knee joints per direct injection or intervertebral discs to express therapeutic proteins, such as interleukin-1 receptor antagonist (IL-1Ra) and luciferase. Containment has been set to BSL-1 and ABSL1.
- The registration was discussed by committee members.
- Training was complete.
- All members were in favor of approval.

- The IBC registration was approved.

16. Gade25-313D-4

- This registration was presented by Dr. Sarah Capasso. This registration is for the generation and/or use of naked plasmid DNA or mRNA for the delivery of genetic constructs encoding fluorescent reporter proteins for characterizing expression and biodistribution profiles, cytokines to modulate anti-tumor immune responses, and metabolic targets involved in cancer therapeutic efficacy and treatment response. This will allow the lab to develop novel gene delivery strategies for hepatocellular carcinoma (HCC) treatment. Constructs will be directly injected into mice or rats or used to modify human or rat cells that are later administered to mice or rats. Cells are from commercial sources or derived from patient samples. Plasmid DNA is from GenScript and the mRNA is from the mRNA Core or other commercial vendors. Containment has been set to BSL-2, ABSL-1, and ABSL-2.
- The registration was discussed by committee members.
- Training was complete.
- All members were in favor of approval.
- The IBC registration was approved.

17. Guo25-296D-4 O-1

18. Guo25-360D-1,4

- These registrations were presented by Ms. Stephanie Adams-Tzivelekidi. Registration 25-296 is for generation and/or use of adeno associated viral vectors with CRISPR/ cas9. IBC 25-360 for the generation and/or use of 4ht generation lentiviral vectors. The lab is engineering regulatory systems that enable injury- or stress-responsive gene expression, using well-characterized endoplasmic reticulum (ER) stress-responsive promoters and enhancers, such as the CHOP gene, which is a key factor for ER stress and reporter genes, like GFP and td tomato which will label this cellular stress. These regulatory elements will detect molecular signatures of cellular stress—such as those induced by injury, ischemia, or neurodegeneration—and activate therapeutic gene expression only when and where it is needed. To validate these systems, they will deliver AAV into animal models of neural injury. Lentiviral vectors or modified cells might be injected into animals via subretinal or intravitreally. CRISPR is used to generate knock out or gene edited cell lines. Containment has been set to BSL-2, ABSL-1, and ABSL-2.
- The registration was discussed by committee members. Dr Daniel Kessler asked for clarification of CRISPR use on the project description of 25-360.
- Training was complete.
- All members were in favor of approval.
- The IBC registration 25-296 was approved. IBC registration 25-360 was approved pending clarification of CRISPR use.

19. Lazar25-332D-4, O-1

- This registration was prepared by Mr. Edwin Siu and presented by Ms. Amanda Wong. This registration is for the generation and/or use of plasmids for *in-vivo* studies. The lab investigates the role of nuclear receptors in transcriptional regulation of metabolism by interacting with

proteins called corepressors to suppress gene expression. One focus is on various corepressors' roles in metabolic diseases; specifically, how metabolic dysfunction-associated steatotic liver disease (MASLD) progresses to hepatocellular carcinoma (HCC). The Lazar lab is proposing to use tumorigenic plasmids, purchased from Addgene, in hydrodynamic tail injection of mice, resulting in HCC tumors forming within 1-2 months after injection. This mouse model will be used to study candidate genes and the putative molecular mechanism that influences this progression in liver disease to cancer. Containment has been set to BSL-1 and ABSL-1.

- The registration was discussed by committee members. Dr. Daniel Kessler requested clarification of CRISPR use in the project description.
- Training was complete.
- All members were in favor of approval.
- The IBC registration was approved pending update to the project description.

20. Linette25-348**D-1,3 O-1**

- This registration was prepared by Mr. Edwin Siu and presented by Ms. Amanda Wong. This registration is for the generation and/or use of 3rd generation lentiviral vectors. The lab focuses on cancer immunology, identifying novel tumor antigens from solid tumors like melanoma and lung cancer. The lab has isolated T cell receptors (TCRs) that recognize tumor-specific peptides and will use lentivirus vectors to express these TCRs in human T cells for functional testing. CRISPR-Cas9 and base editing are used to remove endogenous TCRs or add genes like IL-15, IL-18, or HLA-E, enhancing anti-tumor immunity. The lab will engineer tumor cell lines using lentivirus to express the appropriate components for in vitro functional studies of the modified T cells, enabling the lab to study immune responses to cancer and improve immunotherapies.
- The registration was discussed by committee members. Containment has been set to BSL-2.
- Training was complete.
- All members were in favor of approval.
- The IBC registration was approved.

21. O'Connor25-287**D-1,3,4**

22. O'Connor25-288**D-3,4**

- These registrations were presented by Dr. Tucker Piergallini. Registration 25-287 is for the generation and/or use of 3rd generation lentiviral vectors and registration 25-288 is for the generation and/or use of retroviral vectors with an ecotropic envelope. For 25-287 the lab aims to engineer T cells with transgenes that confer unique metabolic properties to the T cells as they traverse solid tumors with harsh conditions. Replication incompetent lentiviral constructs will be transduced into human T cells. CARs along with other various metabolism genes are transduced. The resulting CAR T cells are infused into NSG mice bearing tumors to analyze the ability of the CAR T cells to reduce/control tumor burden. For 25 -288 the lab aims to uncover novel and innovative genetic approaches to bolster CAR T cell therapies against cancer. The B16.F10 melanoma tumor cell line previously engineered to express human CD19 will be infected with a retrovirus engineered to express human EpCam. The modified tumor cell line will be injected into mice by subcutaneous injection. Mice will then be treated with syngeneic CAR T cells. These CAR T cells are generated by infecting primary mouse T cells with a retrovirus to express a humanCD19 CAR. These cells are also stimulated with the superantigen C215-Fab SEA. The

efficacy of the CAR T cells to control tumor burden will be measured. Containment has been set to BSL-2 and ABSL-2 for 25-287 and BSL-2 and ABSL-1 for 25-288.

- The registration was discussed by committee members. Dr. Daniel Kessler requested the retrovirus name be added to the project description of 25-288.
- Training was complete.
- All members were in favor of approval.
- The IBC registration 25-287 was approved and IBC registration 25-288 was approved pending update to project description.

23. Pack.....25-328 **D-4 E-3 O-1**

- This registration was presented by Dr. Tucker Piergallini. This registration is for the generation and/or use of transgenic Zebrafish. The lab investigates toxin-induced biliary injury using zebrafish models of extra-hepatic biliary atresia (BA). The plant toxin biliatresone, identified by the lab as the cause of naturally occurring BA outbreaks in livestock, is used to model disease mechanisms in vivo. Using Prkg1 and Gucy1a zebrafish mutants to test whether loss of cGMP pathway components increases sensitivity to biliatresone. A transgenic cGMP biosensor line (thPDE5vv) is also used to visualize signaling in biliary cells. Additional experiments involve established lines including Myh11-W506R (Myh11-meltdown) mutants, miR194-GFP-KRASV12D transgenics that express mutant human KRAS in the intestine, and reporter lines krt18-GFP and sm22-GFP that mark biliary and smooth muscle cells, respectively. 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.

24. Schmidt.....25-363**D-4**

- This registration was presented by Dr. Tucker Piergallini. This registration is for the generation and/or use of adeno associated viral vectors. The lab studies opioid use disorders and neurobiological mechanisms underlying drug taking and seeking with the goal to develop new therapeutic approaches to treating substance use disorders. They have shown that GLP-1R agonists and amylin analogs could be re-purposed for treating substance use disorders. Using AAV they will deliver vectors (to brain nuclei using intra-cranial guide cannula) expressing shRNAs and miRNAs to alter GLP-1R and amylin receptor expression in the brain and to express DREADDs in discrete brain nuclei known to regulate drug taking and seeking. This work will allow them to determine cell type-specific responses to GLP-1R agonism and amylin pharmacotherapies. 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.

25. Tabrizi.....25-352D-4 O-1

- This registration was presented by Ms. Stephanie Adams-Tzivelekidi. This registration is for the generation and/or use of modified murine cells into various mouse strains. Circulating nucleic acids such as cell free DNA (cfDNA) and circulating tumor DNA (ctDNA) are found in the plasma and other biofluids of human and animals. Extracellular DNA is involved in immune activation and tumor immune evasion. To understand the impact of these agents on innate sensing pathways for dsDNA (e.g. TLR9, cGAS/STING) and the impact of extracellular nucleases (DNase1L3, DNase 1) on their function, they will administer modified cells to mice to study cfDNA in vivo via subcutaneous injection. The lab is generating those cell lines using Lipofectamine or electroporation; Plasmids and CRISPR/Cas system were purchased from Addgene. Containment has been set to BSL-2, ABSL-1, and ABSL-2.
- The registration was discussed by committee members.
- Training was complete.
- All members were in favor of approval.
- The IBC registration was approved.

26. Uyhazi.....25-319D-4 E-1

- This registration was presented by Ms. Marie-Luise Faber. This registration is for the generation and/or use of adeno associated viral vectors. The lab focuses on developing therapies for inherited retinal degenerations. Currently the lab is working on optimizing gene therapy approaches to treat several additional forms of inherited retinal disease. Since mouse retina contains similar cell types as humans, this is an ideal model to test these therapies. AAV vectors are first tested in 293T cells, 84-31 cells (293 subclones), or Muller glial cells to confirm expression or target genes and ensure correct copies of mutant genes are provided in animal models. Next the vectors will be delivered to the subretinal space of the mouse retina by subretinal injection.
- The registration was discussed by committee members. Containment has been set to BSL-2 and ABSL-1.
- Training was complete.
- All members were in favor of approval.
- The IBC registration was approved.

27. Vahedi.....25-343D-1,4

- This registration was presented by Dr. Tucker Piergallini. This registration is for the generation and/or use of modified *Listeria*. The lab studies how T cell memory develops for use in vaccines. These studies will examine the role of costimulatory and co-inhibitory pathways on the development of anti-viral immunity. They will use the pathogen *Listeria monocytogenes* which has been modified to express known T cell epitopes such as the LCMV GP33 epitopes, and GFP to facilitate tracking and studying the specific immune responses. The agent will be received from the Wherry lab and will be administered to mice via intravenous injection for further study. Containment has been set to BSL-2 and ABSL-2.
- The registration was discussed by committee members.
- Training was complete.
- All members were in favor of approval.

- The IBC registration was approved.

28. Weissman.....25-176D-1,4

- This registration was presented by Ms. Stephanie Adams-Tzivelekidi. This registration is for the generation and/or use of Venezuelan Equine Encephalitis viral vector called T7-VEE-GFP from Addgene with a T7 promotor, GFP reporter gene, and nonstructural proteins (nsP) of VEE. The lab will investigate the efficacy of the saRNA vaccine platform, this viral vector will be used as a template to generate mRNA through in vitro transcription. The mRNA will be encapsulated into LNP as a vaccine to intramuscularly immunize mice to detect the immune response. Self-amplifying RNA (saRNA) has structural similarities to mRNA but includes four additional alphavirus-derived non-structural proteins. These proteins form a replicase that allows the RNA to copy itself inside cells. Because of this built-in amplification, saRNA can achieve stronger immune stimulation with less RNA than standard mRNA. The T7-VEE-GFP saRNA described here encodes Enhanced Green Fluorescent Protein (EGFP) and uses a Venezuelan equine encephalitis (VEE) RNA replicon that lacks structural proteins, making it noninfectious and unable to produce any virus or spread from cell to cell. Containment has been set to BSL-2 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.

29. Zaret.....25-051D-1

- This registration was presented by Stephanie Adams-Tzivelekidi. This registration is for the use of the CytoTune™-iPS 2.0 Sendai Reprogramming Kit from Thermo Fisher. The Zaret lab is investigating global chromatin changes that occur during the reprogramming of somatic BJ fibroblast cells into induced pluripotent stem cells. The kit provides an efficient, non-integrating method for reprogramming through in vitro transduction with Sendai viral vectors delivering the Yamanaka factors (SOX2, KLF4, c-MYC, and OCT3/4). Containment has been set to BSL-2.
- The registration was discussed by committee members. Dr. Daniel Kessler requested that the description of the kit be added to the project description.
- Training was complete.
- All members were in favor of approval.
- The IBC registration was approved pending update to project description.

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

30. Gao.....25-227E-1 O-1

- This registration was presented by Ms. Marie-Luise Faber. This registration is for the generation and/or use of adeno associated viral vectors with CRISPR. The lab is looking to develop safer delivery methods of genomic material, using AAV vectors. AAV is engineered using the CRISPR systems in HEK293T cells to deliver various AAV serotypes. Viral vectors will be used for

transduction in HEK293T cells. Cells will be lysed and the DNA extracted for next-generation sequencing. 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.

SECTION III-E. Experiments that Require IBC Notice Simultaneous With Initiation

31. Ellebrecht.....25-331E-3

- This registration was presented by Ms. Amanda Wong. This registration is for the generation and/or use of transgenic mice. The lab aims to create targeting vectors that can be used to insert the human butyrophilin 3a1 and 2a1 genes into the murine Rosa 26 locus. The human genes will be flanked by loxP sites to allow tissue specific expression of the inserted genes depending on Cre recombinase expression. Butyrophilins have been recently recognized as ligands of human gamma delta T cells. However, mouse gamma delta T cells do not express butyrophilins. The lab aims to express the human ligands in transgenic mice to study human gamma delta T cell biology in a novel mouse model. The linearized pRosa26-PA-butyrophilin targeting vector will be introduced into mouse embryonic stem cells by electroporation (by the Penn Vet Transgenic Mouse Core) Electroporated embryonic stem cells will be cultured under neomycin antibiotic selection to identify cells that have successfully integrated the targeting vector. Correctly targeted embryonic stem cells will be microinjected into mouse blastocysts (early-stage embryos at approximately 3.5 days of development) Blastocysts will be obtained from superovulated donor mice, and Injected blastocysts will be surgically transferred into the uteri of pseudopregnant recipient female mice. Recipient mice will carry the embryos to term. 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.

32. Jordan-Sciutto 25-129..... E-1

- This registration was presented by Ms. Stephanie Adams-Tzivelekidi. This registration is for the generation and/or use of plasmids in E. coli BL21. BL21 cells were purchased from New England Biolabs and are used to produce a fusion protein of a mutant Cas9 and transposase 5, which was purchased from Brain Case. The cells will produce a hybrid protein which will be purified and used in RNA sequencing. The goal of this approach is to multiplex sequence of specific DNA sequences (viral integration, gRNA targets, DNA mutations) and stack with single cell RNA sequencing approaches. Containment has been set to BSL-1.
- The registration was discussed by committee members.
- Training was complete.
- All members were in favor of approval.

- The IBC registration was approved.

33. Lim.....25-357E-1

- This registration was presented by Ms. Amanda Wong. This registration is for the generation and/or use of retroviral vectors with an ecotropic envelope in murine cells. The lab plans to use retroviral vectors packaged in the lab with HEK cells to express MCP-GFP and PCP-GFP to tag MS2 and PP7 stem loops in the mice genome to visualize transcription activity of target genes. This system is used to implement live imaging assays to visualize nascent transcripts in mouse mESCs, T and B cells. The expected outcome is the fluorescent signal of MS2-lacZ and PP7-lacZ gene expression, bound by MCP-GFP and PCP-GFP. 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.

3. New Business:

(a) FDA's New Plausible Mechanism Pathway. (Andrew)

- Dr. Maksymowych shared a publication detailing the FDA's New Plausible Mechanism Pathway.

4. Old Business:

(a) 2026 IBC Meeting Schedule. (Andrew)

- Committee members were reminded that the meeting schedule for 2026 is finalized. No comments were received from the committee disagreeing with proposed meeting dates.

5. End Meeting:

- The Institutional Biosafety Committee was adjourned by Dr. Daniel Kessler at **11:54 AM**.

Our next meeting scheduled for Monday, December 15th, 2025, will be held on site at the EHRS Office with a Teleconference option, at 10:00 am. A light Brunch will be provided.