Institutional Biosafety Committee:

Present: Dr. Steven Albelda, Dr. Jessica Buchanan, Dr. Sara Cherry, Dr. Joseph Fraietta, Dr. Arthur Frank, Dorothy Kaplan, Dr. Daniel Kessler, Dr. Andrew Maksymowych, Dr. Maureen O'Leary, Dr. Claire Mitchell, Dr. David Pegues, Ms. Jessa Yoos

Absent: Dr. Eman Anis, Dr. Paul Bates, Dr. Bruce Freedman, Ms. Denene Wambach

Invited Guests: Ms. Stephanie Adams, Dr. Sarah Capasso, Ms. Marie-Luise Faber, Dr. Tucker Piergallini, Mr. Edwin Siu, Ms. Amanda Wong, Adriana Fraser

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

(A) IBC Member Training: Navigating the ***Penn IBC Electronic Registration System*** [**PIERS**]. (Sarah)

- Dr. Sarah Capasso provided training on navigating the PIERS application. This training was added to the member resources page.

1. IBC Minutes: **12-15-2025**
- 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. Brucker ....**#25-023**.................. **C-1**

Dr. Alexander J Brucker– HGT Protocol Registration Amendment V2...**AMENDMENT**

PROTOCOL TITLE: A Phase 3, Randomized, Double-Masked, Active-Controlled Trial of a Single Intravitreal Injection of 4D-150 in Adults with Macular Neovascularization Secondary to Age-Related Macular Degeneration (4FRONT-1). (Protocol V2 dated December 10, 2025; Master Main ICF V4 dated December 10, 2025; Main ICF dated December 18, 2025.)

IBC #25-023, IRB: 858282, IND #27760, Protocol #4D-150-C003

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

"**Project Overview:** Macular neovascularization (MNV) secondary to neovascular age-related macular degeneration (nAMD) is a retinal condition characterized by rapid loss of central vision. Current standard-of-care for nAMD includes intravitreal (IVT) injections of anti-vascular endothelial growth factor (anti-VEGF) therapies which are safe and effective but require repeated monthly-to-bimonthly administrations to maintain vision. The need for repeated injections can become a substantial burden for some patients and caregivers.

4D-150 is a multi-mechanistic adeno-associated virus (AAV)-based gene therapy product in clinical development for the treatment of nAMD and diabetic macular edema (DME) and is delivered as a single IVT injection.

Specifically, 4D-150 is an adeno-associated virus [AAV] capsid variant [4D-R100] carrying a codon-optimized sequence encoding aflibercept protein [coAFLB] designed to bind VEGF-A, VEGF-B, and PlGF and miRNA targeting VEGF-C).

4D-150-C003 is a Phase 3 multicenter, randomized, double-masked, active-controlled trial in adults with macular neovascularization (MNV) secondary to age-related macular degeneration (nAMD) with no prior exposure to

intravitreal (IVT) anti-vascular endothelial growth factor (anti-VEGF) therapy (i.e., treatment naïve).

Subjects randomized to the 4D-150 arm will receive a single Intravitreal injection of 4D-150 3×10e10 vg in the study eye; subjects randomized to the AFLB arm will receive a sham injection in the study eye. Eligible subjects will be randomized on Day 1 to gene therapy vs afibercept protein. Aflibercept is an anti-VEGF agent approved for the treatment of nAMD globally since 2011. Aflibercept is a recombinant fusion protein consisting of the extracellular domains of human VEGF receptor 1 and 2 fused to the Fc portion of human IgG1. By acting as a soluble decoy for the natural VEGF receptors, aflibercept inhibits their activation, thereby reducing angiogenesis.

The primary efficacy objective is to demonstrate non-inferiority of a single injection of 4D-150 to aflibercept Q8W in the mean change in best-corrected visual acuity (BCVA) from baseline to Week 52.

Agent Description: 4D-150 is comprised of a novel AAV2 capsid variant, 4D-R100, carrying two components: (1) miRNA targeting VEGF-C (miR-(VEGF-C)) and (2) codon-optimized sequence encoding aflibercept protein (coAFLB) that binds VEGF-A, VEGF-B, and placental growth factor (PlGF). Both transgenes are contained within a single transgene cassette and under the control of a ubiquitous promoter

Product is produced in the GMP suite of 4D Molecular Therapeutics

Specifically, 4D-150 (4D-R100.CAG-miR-(VEGFC)-coAFLB) comprises:

- Capsid: AAV capsid variant (4D-R100)
- CAG promoter: (C) cytomegalovirus (CMV) immediate-early enhancer element, (A) first

  exon and the first intron of chicken beta-actin gene, (G) splice acceptor of the rabbit betaglobin gene.
- Payload:
  - o codon-optimized transgene encoding the aflibercept protein which binds VEGFA, VEGF-B, and PlGF
  - o micro-RNA (miRNA) targeting expression of VEGF-C, placed within the chicken beta-actin intron of the CAG promoter..

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

Gene transfer agent delivery method: Intravitreal injection

4D-150 (3 ×10e10 vg) will be administered as a single dose (50 µl) IVT injection in the study eye on Day 1.

Intended target: The 4D-R100 capsid was identified through directed evolution for robust delivery of transgenes to the primate retina following IVT administration, the intended clinical route of administration. 4D-R100 has the capacity to transduce all major cell types across all regions of the primate retina and multiple retinal layers, including RPE cells, photoreceptors, and RGCs in the periphery, midperiphery, and macular regions following IVT administration.

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

Preclinical Studies: Available Phase 2 clinical data shows that a single IVT injection of 4D-150 continues to be safe and well tolerated with encouraging signs of clinical activity, including stability in mean best corrected visual acuity (BCVA) and central subfield thickness (CST) changes through Week 24.

Initial clinical trial data from an ongoing Phase 1/2 trial (4D-150-C001, NCT05197270) in >130 subjects with nAMD and up to 2-years follow-up, suggest that a single IVT injection of 4D-150 exhibits a favorable safety profile. No severe treatment-emergent adverse events (TEAEs), dose-limiting toxicities, or serious adverse events (SAEs) related to 4D-150 have been observed.

Potential for shedding: Minimal

Amendment: This protocol has previously been approved. The purposes of this amendment are:

- Implementation of a masked, independent Supplemental Injection Review Committee (SIRC) to verify Disease Activity Criteria
- Clarified guidance for intraocular inflammation (IOI) reporting and updated definition of an Adverse Event of Special Interest (AESI) of ocular inflammation

Additional clarifications include:

- Sample size increase from 400 to 480 to align with study power of >90%
- Aflibercept injection during the run-in period may be administered prior to Reading Center confirmation
- Tonometry guidance
- Corticosteroid dose modification guidance
- Standard-field image collection guidance in the case of clinically significant IOI
- Prophylactic anterior chamber paracentesis is not permitted
- Reporting period of Medical History vs. Adverse Events (AEs)
- Removal of reference to units of measure for height
- SD-OCT may be performed prior to pupil dilation
- Day 1 samples are to be analyzed to assess immunogenicity

None of these increases any biosafety risk.s.

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.

2. Chapin............**#23-153**................. **C-1**

Dr. William J Chapin– HGT Protocol Registration Amendment V7 ....**AMENDMENT**
PROTOCOL TITLE: UPCC 12223: A Phase 2, Open-label, Multicenter Study Investigating RP2 Oncolytic Immunotherapy in Combination with Second-line Therapy in Patients with Locally Advanced Unresectable, Recurrent and/or Metastatic Hepatocellular Carcinoma. (Protocol V7 dated October 10, 2025; Main ICF dated November 25, 2025.)
IBC #23-153, IRB #854065, IND #028278, UPCC #12223, Protocol #RP3-003

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

"**Project Overview:** Despite advances in treatment for unresectable hepatocellular carcinoma (HCC) and biliary tract cancers (BTC), few patients achieve durable benefit, and long-term survival rates remain poor.

The purpose of the study is to assess the efficacy and safety of RP2, a selectively replication competent herpes simplex virus type 1(HSV-1)-based oncolytic immunotherapy, in combination with atezolizumab plus bevacizumab in patients with locally advanced unresectable, recurrent, and/or metastatic HCC, and in combination with durvalumab in patients with unresectable locally advanced or metastatic BTC.

This amendment changes the dosing regimen for RP2 after the first 4 doses from every 3 weeks to every 2 weeks. Patients who were enrolled in the HCC cohort prior to this amendment will be switched over to the every-2-weeks dosing schedule for RP2, and for atezolizumab and bevacizumab when given in combination with RP2, if deemed by the investigator to be in the best interest of the patient. Additionally, two new cohorts have been added: a new HCC combination therapy cohort and a new HCC RP2 monotherapy cohort. The rationale for adding the monotherapy cohort is that 1) in a separate study, RP2 provided objective clinical responses in patients with advanced solid tumor malignancies when given as a single agent, and 2) administration of RP2 as a single agent will help evaluate potential single agent activity in patients with HCC whose disease has progressed after approved first-line immune-based treatment.

Agent Description: RP2, rHSV-1hGM-CSF/ ahCTLA-4/GALV. RP2 is a preparation of a genetically modified live herpes simplex 1 virus cultured in Vero cells. RP2 is a selectively replication competent, acyclovir-sensitive HSV-1 that is intended for direct injection into suitable solid tumors. RP2 was constructed using a new isolate of HSV-1 (strain RH018). The virus was modified by deleting the genes encoding HSV-1 neurovirulence factors ICP34.5 and ICP47 and adding an expression cassette encoding the hGM-CSF gene, the coding sequence for GALV-GP with the R sequence deleted, and the sequence for a single chain antibody-like molecule to human CTLA-4.

It consists of 1) a lipid bilayer envelope derived from host cell membranes, including polyamines, lipids, and glycoproteins; 2) a tegument of amorphous material; 3) a capsid made of capsomers arranged in icosapentahedral symmetry; and 4) an internal core containing double-stranded DNA of ~160 Kb pair.

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

Gene transfer agent delivery method: RPS is administered into non-neurological solid tumors by direct or image-guided intratumoral injection.

Intended target: Tumor cells.

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

Potential for shedding: Biodistribution and shedding of RP2 is an exploratory objective in this study, but previous measures indicate the likelihood of dissemination of RP2 DNA to external environment is minimal.

Amendment: The previous HCC Cohort is now identified as Cohort 1a. The HCC Cohorts include the following:

–Cohort 1a: RP2 (Q2W and Q3W) in combination with atezolizumab and bevacizumab. (This cohort is closed to further enrollment.)

–Cohort 1b: RP2 (Q2W) in combination with atezolizumab and bevacizumab.

–Cohort 2: RP2 monotherapy (Q2W).

The BTC Cohort is now identified as Cohort 3..

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. Cohen ....#**26-003** **C–1**
Dr. Adam D Cohen– NEW HGT Protocol Registration ....**FULL REVIEW**
PROTOCOL TITLE: UPCC 39422 Intermediate-Size Population Expanded Access Program (EAP) for Ciltacabtagene autoleucel (cilta-cel) Out-of-Specification (OOS) in patients with Multiple Myeloma. (Protocol V4 dated September 20, 2025; Main ICF dated June 24, 2025.)
IBC #26-003, IRB #852647, IND #18080, UPCC #39422, Protocol #68284528MMY4006

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

  "**Project Overview:** The purpose of this expanded access program (EAP) is to provide ciltacabtagene autoleucel (cilta-cel) that does not meet the commercial release specifications of CARVYKTI and is not available via the local health care system in the country where the treatment is requested. Plan to infuse product in Apheresis with CHPS inpatient used as a back up. Access to cilta-cel OOS may be considered for patients when re-apheresis, re-manufacturing, or other anti-myeloma directed therapy is not considered feasible or adequate per investigator

  Agent Description: Cilta-cel therapy is a BCMA-directed genetically modified autologous T cell immunotherapy that involves reprogramming a patient's T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate BCMA-expressing malignant and normal cells.

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

  Gene transfer agent delivery method: Infusion of IP.

  Intended target: Multiple Myeloma. Relapsed or refractory multiple myeloma.

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

  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 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. Frank..............#**26-004** **C–1**
Dr. Ian Frank– NEW HGT Protocol Registration...**FULL REVIEW**
PROTOCOL TITLE: HVTN 322: A phase 1 clinical trial to evaluate the safety and immunogenicity of the V2 apexdirected immunogens DV201P-RNA and DV202B1-RNA in adult participants without HIV. (Protocol V1 dated December 8, 2025; Main ICF dated January 5, 2026.)
IBC #26-004, IRB #pending, IND # 032324, Protocol# HVTN 322

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

  "**Project Overview:** This Phase 1, open-label clinical trial tests investigational mRNA-LNP HIV-1 Env immunogens (DV201P-RNA and DV202B1-RNA) designed to initiate V2 apex broadly neutralizing antibody precursor responses. The primary objectives are to assess safety/tolerability and to characterize early V2 apex-specific B-cell and antibody responses after priming and boosting. The protocol includes intensive immunogenicity sampling (including leukapheresis and axillary lymph node fine needle aspiration) in healthy adult participants without HIV.

  Agent Description: Non-viral delivery of modified mRNA encapsulated in lipid nanoparticles (LNP) for in vivo expression of HIV-1 Env gp150 transmembrane trimers (DV201P-RNA and DV202B1-RNA).

  LNP formulation contains DSPC, plant-derived cholesterol, an ionizable cationic lipid, and a PEG-2000 lipid; mRNA is translated in cells that take up the mRNA-LNP, producing membrane-anchored Env trimers.

  DV201P-RNA encodes CAP256 transmitted/founder Env (OPT4) with engineered modifications (e.g., N130 glycan removal; variable-loop substitutions; stabilization). DV202B1-RNA encodes the same gp150 Env plus R189T to introduce an N187 glycan intended to shield an off-target V2 glycan hole.

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

Gene transfer agent delivery method: Intramuscular administration as a bilateral split dose (two 0.5 mL deltoid injections; 1.0 mL total) at 50, 100, or 150 mcg per vaccination depending on group and timepoint.

Intended target: In vivo local cells that take up the mRNA-LNP (primarily myocytes and antigen-presenting cells) at the injection site; expressed gp150 Env trimers are intended to prime/boost V2 apex bnAb-precursor B cells. Transduction efficiency is not applicable (non-replicating, non-integrating platform).

Other material to be used in preparation of the agent: No helper virus or replication-competent vector; product is supplied as formulated mRNA-LNP.

Dilute with 0.9% sodium chloride (USP) under aseptic technique in a Class II biosafety cabinet; discard unused material as biohazard waste per institutional policy.

Preclinical Studies: Mouse and rhesus macaque studies demonstrated the regimen was well tolerated and elicited V2 apex-directed immune responses.

GLP rat toxicology with related HIV Env mRNA-LNP vaccines (same LNP formulation) showed transient inflammatory findings that resolved during recovery.

Potential for shedding: No replication-competent agent; shedding or secondary transmission is not expected. Standard Precautions/BSL-2 practices are appropriate.

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.

5. Schuster..........#**25-398**................. **C–1**

Dr. Stephen J Schuster– NEW HGT Protocol Registration ....**FULL REVIEW**
PROTOCOL TITLE: UPCC 30425: Phase 1 Study of huCART19-IL18-eDHFR Cells in Patients with Relapsed or Refractory Follicular Lymphoma. (Protocol V2 dated September 12, 2025; Mian ICF dated November 13, 2025.)
IBC #25-398, IRB #859859, IND # 31902, Sponsor# 30425

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

"**Project Overview:** This is a phase 1, open-label study to evaluate the feasibility, safety and preliminary efficacy of huCART19-IL18-eDHFR cells administered in patients with relapsed or refractory follicular lymphoma. Co-expression of eDHFR within huCART19-IL18 cells will allow the trafficking of the transduced CAR T cells to be visualized by PET/CT imaging using an investigational radiolabeled imaging agent [18F]Fluoropropyl-Trimethoprim. The feasibility of using [18F]FP-TMP PET/CT imaging to detect and measure the eDHFR-expressing CAR T cells will be investigated, as well as its ability to provide insight into CAR T cell pharmacokinetics, biodistribution, and persistence.

This study will be initiated as a single arm study (Treatment Arm A), which will evaluate the use of huCART19-IL18-eDHFR cells without prior lymphodepletion. Adult patients ages ≥ 18 with CD19+ relapsed or refractory follicular lymphoma. Up to 6 evaluable subjects. All subjects who receive huCART19-IL18-eDHFR cells and complete at least one post-infusion [18F]FP-TMP PET/CT scan will be considered evaluable for the primary outcome measure of imaging feasibility. Additional treatment arms may also be introduced in the future, via subsequent amendment(s).

All subjects will receive a single flat dose of 7x106 huCART19-IL18-eDHFR cells. This is the recommended dose for expansion identified for huCART19-IL18 cells. However, as the CAR T cells used in this study will also co-express eDHFR, subjects will be monitored for treatment-limiting toxicities on a rolling basis. In the event ≥ 2 TLTs are identified at any time, treatment activity will be paused to allow for a cumulative safety review and a decision regarding possible dose de-escalation to 3x106 cells.

Subjects will undergo exploratory imaging with [18F]FP-TMP PET/CT scans pre- and post-infusion to assess the feasibility of detecting and monitoring the eDHFR-expressing CAR-T cells. Subjects will also be evaluated for disease response using standard FDG PET/CT imaging at Month 3 following cell administration. Subjects with a complete response to the huCART19-IL18-eDHFR cells will continue to be followed in primary follow-up as per routine care without intervening treatment. Subjects who have progressive disease post-treatment will transition into long-term follow-up. Subjects with a best response of partial response or stable disease after initial treatment with huCART19-IL18-eDHFR cells are eligible to receive retreatment, if determined clinically appropriate.

During retreatment, eligible subjects will receive another infusion of huCART19-IL18-eDHFR cells following lymphodepleting chemotherapy. The same dose of huCART19-IL18-eDHFR cells received as part of initial treatment will be administered during retreatment unless the subject experienced a treatment-limiting toxicity at that dose level, or the dose was formally de-escalated based on all observed data at that dose level.

Agent Description: huCART19-IL18-eDHFR cells are genetically modified autologous T cells engineered by co-

transduction with two lentiviral vectors; one vector expressing a chimeric antigen receptor (CAR) targeting the CD19 antigen and human Interleukin 18, and a second vector expressing E.coli dihydrofolate reductase.

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

Gene transfer agent delivery method: Single IV gravity drip infusion of huCART19-IL18-eDHFR.

Intended target: CD19-positive follicular lymphoma cells.

Other material to be used in preparation of the agent: Manufacturing and Formulation: huCART19-IL18-eDHFR 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 an LVV to express the CD19-binding motif and IL18 and a second LVV to express eDHFR and expanded for 4 days. The cells are then washed and concentrated to make huCART19-IL18-eDHFR, which is a cryopreserved liquid cell suspension intended for intravenous infusion.

Preclinical studies: N/A

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

6. Susanibar-Adaniya .**#25-385** **C-1**
Dr. Sandra P Susanibar-Adaniya– NEW HGT Protocol Registration..**FULL REVIEW**
PROTOCOL TITLE: UPCC 64425 A Phase 1/2, Open-label, Multicenter Study of mRNA-2808 in Participants with Relapsed or Refractory Multiple Myeloma. (Protocol V1 dated May 13, 2025; Main ICF dated November 5, 2025.)
IBC #25-385, IRB # 859896, IND # 31061, Protocol# mRNA-2808-P101

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

"**Project Overview:** Despite advances in multiple novel drug classes, MM remains incurable. Leveraging its proprietary mRNA platform, the Sponsor has developed mRNA-2808, a multiplexed, mRNA-encoded T-Cell Engager.

In MM and other cancers, tumor heterogeneity presents a substantial challenge, often requiring multi-agent treatment strategies to improve patient outcomes and potentially achieve a cure. Therapies involving T-Cell Engagers that target a single Tumor Associated Antigen can initially yield high Objective Response Rates. However, resistance frequently emerges, commonly due to mechanisms related to the specific tumor antigen. Targeting multiple Tumor Associated Antigens simultaneously offers a promising approach to counteract resistance and potentially boost therapeutic effectiveness.

Overall Design Synopsis: This is a First in Human, Phase 1/2, open-label, multicenter, dose-escalation study to determine the safety, Pharmo Kinetics, PharoDynamics, and preliminary efficacy of mRNA-2808 in participants with Multiple Myeloma.

The purpose of this study is to evaluate the safety and tolerability of mRNA-2808 and to determine the RP2D(s) in participants with MM. The study will be conducted in 2 parts: Part 1 will be Dose Escalation and Part 2 will be Dose Expansion.

The study plans to evaluate approximately 8 Dose Levels of mRNA-2808. The starting dose will be 0.002 mg/kg administered IV. Subsequent dose levels will be selected based on all available data including, but not limited to, safety, PK, PD, and efficacy. Multiple dose levels and/or alternative dosing regimens may be explored to determine one or more Recommended Phase 2Doses(s).

In summary: For each Part, the study will be divided into 3 periods: Screening, Treatment, and Follow-up. The Screening Period will start on the day of signing of the Informed Consent Form and will have a maximum duration of 28 days. Eligible participants will receive the study treatment for a Treatment Period of up to 12 cycles (approximately 1 year). The Follow-up Period begins upon permanent discontinuation of study treatment at any time, with a Safety Follow-up Period of 30 days. mRNA-2808 will be administered IV over 10 minutes.

ModernaTX, Inc. (the Sponsor) is developing mRNA-2808, an mRNA-encapsulated LNP-based therapeutic designed for participants with MM. mRNA-2808 is comprised of 4 mRNAs: anti-GPRC5D HC×anti-CD3, anti-FcRH5 HC×anti-CD3, anti-BCMA HC×anti-CD3, and an anti-HSA common LC×anti-CD3 to increase circulating half-life. These mRNAs encode 3 distinct bispecific T-Cell Engagers that target clinically validated Tumor Associated Antigens and selectively engage and activate T cells, promoting T cell-mediated cytotoxicity of tumor cells.

Agent Description: Encapsulated mRNA..

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

Gene transfer agent delivery method: Infusion.

Intended target: Tumor Cells.

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

Preclinical studies: Preclinical pharmacology studies demonstrated that mRNA-2808 provides robust, dose-dependent, on-target cytotoxicity against Tumor Associated Antigens-positive cancer cells in vitro and ex vivo, exhibits potent antitumor efficacy in multiple tumor-bearing Multiple Myeloma mouse models, and demonstrates substantial pharmacological activity in monkeys. In vitro pharmacology studies demonstrated that the T-Cell Engagers encoded by mRNA-2808 bind specifically and with high affinity to their target antigens on MM cells and CD3 on T cells. Specifically, in vitro and ex vivo studies showed selective cytotoxicity against Tumor Associated Antigens-positive MM cell lines and patient-derived malignant plasma cells.

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

7. Tanyi ....**#26-013** **C-1**
Dr. Janos L Tanyi – NEW HGT Protocol Registration..**FULL REVIEW**
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 V6 dated March 11, 2025; Main ICF V5 dated December 17, 2025; Out of Specification ICF dated November 19, 2025.)
IBC #26-013, IRB #852470, IND #28693, PROTOCOL #STAR-101

- Dr. Daniel Kessler introduced the submission.
- Dr. David Pegues 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 dose of SynKIR-110 administered to subjects with mesothelin-expressing advanced ovarian cancer, mesothelioma, and cholangiocarcinoma. Mesothelin is a cell surface protein which has limited expression in normal mesothelial-derived tissues and on some lung epithelial and immune cells but is overexpressed and considered as a tumor-associated antigen in many solid tumors.

Agent Description: SynKIR-110 is multichain CAR that is designed to replicate the natural multichain activating killer immunoglobulin like receptors (KIRs), which are an important family of immunologic receptors used by T cells and natural killer cells. SynKIR-110 is comprised of autologous T cells transduced with a chimeric receptor that consists of a human DAP12 adaptor protein (DNAX activating protein of 12 kDa), the mesothelin-binding SS1 small chain variable fragment fused to a truncated KIR2DS2 (KIRS2) transmembrane and cytoplasmic domain. The receptor and DAP12 proteins are separated by a thosea asigna virus 2A (T2A) ribosomal skip sequence. This multichain immunoreceptor is designed to preserves CAR T cell anti-tumor functionality in the solid tumor microenvironment, and it improved potency in vivo in mouse models when compared with single-chain CAR designs.

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

Gene transfer agent delivery method: Autologous T cells activated with anti-CD3/CD28 Ab-coated beads and then transduced with a 3rd generation self-inactivating lentiviral vector containing the SynKIR-110 transgene (DAP12-T2A-SS1-KIRS2.

Intended target: Ex vivo autologous T cells. CAR/KIR T cells showed similar transduction efficiencies by SS1 scFv staining, with KIR-CAR and CD3ζ-based CAR transduced to 95% and 81%, respectively.

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

Preclinical studies: N/A.

Study progress: As of 16-Sep-2025, 14 subjects have been treated with SynKIR-110 across 4 cohorts in the ongoing STAR-101 Study. Three subjects received an IV administration of 1 × 10^7 viable transduced cells/m2 as part of Cohort 1, 3 subjects received 3 × 10^7 viable transduced cells/m2 as part of Cohort 2, 4 subjects received 1 × 10^8 viable transduced cells/m2 as part of Cohort 3, and 4 subjects received 3 × 10^8 viable transduced cells/m2 as part of Cohort 4.

All 14 subjects treated with SynKIR-110 had advanced disease: (ovarian (8), fallopian tube (1), primary peritoneal-ovarian (1), pleural epithelial mesothelioma (3), and cholangiocarcinoma (1)). 13 subjects were female (age range,

54-70 yr). 5 subjects were continuing in the study, and 9 subjects discontinued the study (5 due to clinical progression and 1 subject each to voluntary withdrawal, an AE, transfer to hospice, and death due to Grade 5 sepsis).

All 14 subjects treated in Cohorts 1-4 in the STAR-101 Study had treatment-emergent adverse events (TEAEs) related to SynKIR-110. Eight subjects experienced SAEs, including 6 episodes of cytokine release syndrome (Grade 1-2), 2 episodes of febrile neutropenia (related to administration of cyclophosphamide and fludarabine), and 1 episode each of encephalopathy (Grade 3), respiratory failure (Grade 4), and sepsis/death (Grade 5).

The informed consent form (version 11/17/25) reflects both known and potential risks of CAR therapy and administration of lymphodepletion with cytotoxic chemotherapy.

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 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: #18 **Research Administrative Actions: #29**

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

8. Chen..............26-001...........**D-4**

- The registration was presented by Dr. Tucker Piergallini. This registration is for the generation and/or use of mRNA and siRNA LNPS. The lab will generate non-viral lipid nanoparticles with mRNA and siRNA for transfection of mammalian cells and implantation into animals. The lab is investigating local delivery of mRNA and siRNA to bone and gingival tissues. For in-vitro experiments, primary mouse or human cells are transfected by RNA-LNPs. For in-vivo experiments, immunodeficient NOD/SCID mice are transplanted with tdROSA bone marrow MSCs, bone graft materials, and LNPs with Cre mRNA to assess whether the bone graft materials can deliver the LNPs and result in genetically labeled bone in vivo. In other pilot studies, Cre-mRNA LNPs are injected into cranial bone tissues of TdROSA mice to assess whether the local injections can result in genetically labeled cranial bone cells. This project utilizes several RNA targets to develop this technology and perform preclinical studies in vivo in mice and with human explant tissue and human cells, including firefly luciferase mRNA, Cre recombinase mRNA, FGF2 mRNA, NFKBIZ siRNA, and STAT3 siRNA. Containment has been set to BSL-1, -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

9. Chen..............25-389...........**D-1,3 O-1**

- The registration was presented by Ms. Stephanie Adams-Tzivelekidis. This registration is for the generation and/or use of 3rd generation lentiviral vectors. IBC registration 25-391 is for AAV and registration 25-390 is for the generation and/or use of B-strain E. coli expressing the above vectors. Registrations are for the use of CRISPR/Cas9 in human and murine stem cells. Viral

vectors will be utilized for gene delivery and genome editing studies aimed at understanding and optimizing molecular mechanisms of CRISPR-based genome editing and transgene expression in mammalian cells. The goal is to evaluate how Lentivirus or AAV-delivered genetic payloads (including reporter genes, CRISPR guide RNAs, and genome editing donor templates) behave in different mammalian cell types to support the development of improved genome engineering tools. Containment for 25-389 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. Goodman........25-339............**D-1,3,4**

11. Goodman........25-340............**D-4, O-1**

12. Goodman........25-341............**D-4, O-1**

13. Goodman........25-342............**D-4, O-1**

- The registrations were presented by Ms. Amanda Wong. These registrations are for the generation and/ or use of 2nd generation lentiviral vectors (339), adeno associated viral vectors with CRISPR/Cas9 (340), naked non-viral DNA with CRISPR/Cas9 (341), and genetically modified cells with CRISPR/Cas9 (342). The lab's focus is on anti- tumor therapy and will use 2nd generation lentiviral vectors, AAV w/ CRISPR, naked DNA w/ CRISPR, or modified cells to deliver chimeric antigen receptors (CARs), barcodes, and related genetic elements into primary human T cells, and in some experiments other primary human immune cells (primary PBMCs, Jurkat cells). Genes of interest include CAR constructs with natural or synthetic intracellular domains, fluorescent or epitope tags for tracking, and in some cases transcription factors or regulatory elements intended to modulate immune cell function. These studies aim to understand how receptor signaling and other genetic programs affect immune cell behavior, persistence, and therapeutic potential. Target recipients are isolated human immune cells obtained from commercial vendors or institutional core facilities. In some studies, engineered cells may be administered to immunodeficient mice for preclinical evaluation of persistence and anti-tumor activity using standard routes such as intravenous or intratumoral injection under approved animal protocols. Containment has been set to BSL-2 and ABSL-1, -2.
- The registration was discussed by committee members. Dr. Daniel Kessler noted issue with reasoning for use of 2nd generation lentivirus and requested more appropriate language. Dr. Sarah Capasso requested addition of ABSL-1 designation for 3 of the registrations.
- Training was complete.
- All members were in favor of approval.
- The IBC registrations were approved pending changes.

14. Markmann......25-392............**D-1,3,4**

15. Markmann......25-397............**D-4**

- The registrations were presented by Ms. Stephanie Adams-Tzivelekidis. IBC 25-392 is for the generation and/or use of replication-deficient third-generation lentiviral vectors acquired from a commercial vendor for transduction into NHP MSCs (non-human primate mesenchymal stromal cells). The resulting modified MSCs will be expressing immunomodulatory and vasculogenic

factors (including FasL, PD-L1, IL-10, CD47, and VEGF) and will be administered to recipient mice via intravenous (tail vein) injection or subcutaneous administration or co-transplanted with islets for in vivo transplantation tolerance studies. IBC 25-397 is for the generation and/or use of MMLV with an ecotropic envelope acquired from a commercial vendor. The retrovirus encoding a chimeric antigen receptor (CAR) and used for transduction into primary murine splenic B cells. The resulting engineered CAR-B cells will be administered to recipient mice via intravenous (tail vein) injection and co-transplanted with islets for in vivo transplantation tolerance studies. Containment has been set to BSL-1, -2 and ABSL -1, -2.

- The registration was discussed by committee members. Dr. Daniel Kessler requested the project description be updated to include mice as a possible target.
- Training was complete.
- All members were in favor of approval.
- The IBC registrations were approved pending update to project description.

16. Robertson.......25-404............**D-1**

- The registration was presented by Dr. Sarah Capasso. This registration is for the generation and/or use of retroviral-based (pBABE - MMLV), non-replication-competent plasmid construct for the overexpression and/or knockdown of CENPB in human cell culture. CENPB is a kinetochore-associated protein involved in chromosome segregation. This will allow the lab to study its role in Kaposi's sarcoma-associated herpesvirus (KSHV) episome maintenance (knockdown may reduce KSHV episome copy number). Human cells will be infected with wild-type, unmodified KSHV OR cells may already harbor latent KSHV infection. Work will be done in cell culture only. The virus will not be modified. Altered maintenance of KSHV episomes will be evaluated using quantitative PCR and fluorescence-based assays. 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

17. Tchou.............24-202............**D-1,3**

- The registration was presented by Mr. Edwin Siu. The registration is for the storage of 3rd generation lentiviral vectors. The lab has previously modified murine breast cancer cells to express Luc/GFP with 3rd gen lentivirus. The modified cells were intended for implantation in mice to generate tumors observable via bioluminescent imaging techniques. No experiments are currently planned with the modified cell lines, and they are in cryopreserved storage only. The previously described 3rd gen lentiviral vector is no longer in use, and the lab does not possess any stocks of the vector. 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

18. Wolfe ....25-402...........**D-1,4**

- The registration was presented by Dr. Sarah Capasso. This registration is for the generation and/or use of 3rd generation lentiviral vector expressing eGFP in research cats. This will allow the lab to evaluate the use of lentiviral vectors to express larger proteins in the treatment of ultra-rare human monogenic disease. The 3rd generations vectors will be delivered to research cats via the CSF and the distribution of eGFP in the brain will be evaluated. Containment has been set to BSL-2 and ABSL-1, -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–O. Experiments that Require IBC Approval <u>Before</u> Initiation:

19. Chen..............25-391...........**E-1, O-1**

- The registration was presented by Ms. Stephanie Adams-Tzivelekidis. This registration is for the generation and/or use of 3rd generation lentiviral vectors. IBC registration 25-391 is for AAV and registration 25-390 is for the generation and/or use of B-strain E. coli expressing the above vectors. Registrations are for the use of CRISPR/Cas9 in human and murine stem cells. Viral vectors will be utilized for gene delivery and genome editing studies aimed at understanding and optimizing molecular mechanisms of CRISPR-based genome editing and transgene expression in mammalian cells. The goal is to evaluate how Lentivirus or AAV-delivered genetic payloads (including reporter genes, CRISPR guide RNAs, and genome editing donor templates) behave in different mammalian cell types to support the development of improved genome engineering tools. Containment for 25-391 has been set to BSL-1 and -2.
- The registration was discussed by committee members.
- Training was complete.
- All members were in favor of approval.
- The IBC registration was approved

20. Lampson ....25-383...........**E-3, O-1**

- The registration was presented by Dr. Sarah Capasso. This registration is for the creation of transgenic mice by the Transgenic and Chimeric Mouse Facility using CRISPR/Cas9 technology. The first mouse model will carry mouse artificial chromosomes (MAC) which will allow the lab to develop new tools for fundamental chromosome research. The second mouse model will carry a modified CENP-A gene to evaluate the functional consequences on the recruitment of protein subunits of the constitutive centromere associated network (CCAN). 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-E. Experiments that Require IBC Notice Simultaneous With Initiation

21. Bugaj.............25-305...........**E-1**

- The registration was presented by Ms. Stephanie Adams-Tzivelekidis. This registration is for the use and generation and/or use of E. coli BL21 was used in the production BcLOV4-mCherry. This protein was then purified via a HIS-Tag and tested for its light sensitivity isolated from other cellular components. BcLOV4: BcLOV4 is a unique bi-functional photoreceptor protein from the fungus Botrytis cinerea that is widely used as a single-component optogenetic tool. It responds dynamically to both blue light and temperature by simultaneously clustering and translocating to the plasma membrane. 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

22. Chen..............25-390...........**E-1**

- The registration was presented by Ms. Stephanie Adams-Tzivelekidis. This registration is for the generation and/or use of 3rd generation lentiviral vectors. IBC registration 25-391 is for AAV and registration 25-390 is for the generation and/or use of B-strain E. coli expressing the above vectors. Registrations are for the use of CRISPR/Cas9 in human and murine stem cells. Viral vectors will be utilized for gene delivery and genome editing studies aimed at understanding and optimizing molecular mechanisms of CRISPR-based genome editing and transgene expression in mammalian cells. The goal is to evaluate how Lentivirus or AAV-delivered genetic payloads (including reporter genes, CRISPR guide RNAs, and genome editing donor templates) behave in different mammalian cell types to support the development of improved genome engineering tools. Containment for 25-389 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

23. Daniell...........25-298...........**E-2**

- The registration was presented by Dr. Sarah Capasso. This registration is for the creation and/or use of transgenic plants (lettuce and tobacco) using gene gun delivery of plasmids loaded onto gold nanoparticles (a.k.a.: particle bombardment). Recombinant plants are screened for the modifications by expression of antibiotic marker and selected for maternal inheritance and stability in passing the gene to subsequent generations. Plants are grown in growth chambers in the lab location in Levy Building and in greenhouse at the Pennovation Center for seed production. This will allow the lab to develop an oral delivery system for protein drugs like human autoantigens for prevention of Type 1 Diabetes, myelin basic protein for reduction of amyloid plaques in Alzheimer's disease, and enzymes for various nontherapeutic use, such as for biofuel and food industry. Safety measures include covering flowering parts with a mesh bag to

prevent seed dispersal and discarding plant waste through the biohazardous waste stream. Containment has been set to BSL-1 and PBSL-1.

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

24. Vining ....25-381 ....**E-1**

- The registration was presented by Dr. Tucker Piergallini. This registration is for the generation and/or use of non-viral lipid nanoparticles with mRNA and siRNA for transfection of mammalian cells. They are investigating local delivery of mRNA and siRNA to bone and gingival tissues and cells for the goal of developing an immunomodulatory regenerative material. For in vitro experiments, mouse and human cells are treated with the LNPs.siRNA is purchased from Dharmacon (Horizon Discovery). mRNA is purchased from Trilink Biotechnologies. We are discussing obtaining custom FGF2 mRNA from the Penn Biofoundry Pilot Award. Containment has been set to BSL-1, -2.
- The registration was discussed by committee members
- Training was not complete.
- All members were in favor of approval.
- The IBC registration was approved pending completion of training.

3. New Business:

(a) No New Business Scheduled.

4. Old Business:

(a) No Old Business Scheduled.

5. End Meeting:

- The Institutional Biosafety Committee was adjourned by Dr. Daniel Kessler at **11:32 AM**.

Our next meeting scheduled for Monday, February 23rd, 2026, will be held on site at the EHRS Office with a Teleconference option, at 10:00 am. A light Brunch will be provided.