NIH Institutional Biosafety Committee Minutes
Location: Bethesda Main Campus
September 03, 2025
2:00 PM – 5:00 PM
Virtual via Microsoft Teams

Members present: (12)
Quorum met: Yes

Harry Malech, Chair, clinician	Stephen Denny, animal research expert*	Alicia Alexion, unaffiliated member
Richard Baumann, BSO	Clevetta Drew, unaffiliated member	Michael Kujawa, ABSO
Bridgette Billioux, clinician, virology	Luz Angela Rosas, Laboratarian	Steve Whitehead recombinant and molecular techniques, virology
Robert Craigie, recombinant and molecular techniques	Stephanie Goff, Clinician	Althea Treacy, Biorisk Branch Chief

- absent members: Emily Lee
*Provided comments *in absentia* for select secondary reviews

Guests present (9)

Rebecca Anderson (RML)	Howard Parnes (for Dr. Pinto)	Kaitlyn Connors
Grace Markley	Jocelyn Mendoza	Theresa Bell (NCI at Frederick)
Camellia Banerjee	Luca Giurgea	Diego Valdez-Oranday

Announcements & Call to Order

The meeting was called to order by Dr. Malech at 2:04 PM.

Review of the Past IBC Meeting Minutes

09 July 2025 Minutes

a. Comments on minutes, as applicable
b. The minutes were unanimously approved with minor modifications and formatting corrections.

New Committee Business

I. BSO preliminary registration approvals since the previous meeting

a. Pathogen registrations (11 total): 25-BMC-131, -133, 137-139, -144, -149, -151, -152, -154, -157
b. rDNA and rDNA/pathogen registrations: 25-BMC-132 (Jin) III-D-3-a - Compatibility Study of MMA-101(rAAV) with device. (no cell or animal work), 25-BMC-134 (Philpott) III-D-3-a/ III-D-4-a- AAV for the study of iron chaperones in mice. This registration updates and replaces registrations RD-18-IV-07 and 7372 previously reviewed by the NIH IBC, 25-BMC-135 (Zhang) III-E-1- Structural basis of double-stranded RNA recognition by RNase V1, 25-BMC-136 (Singer) III-E-1- Roles of BRD4 histone acetyltransferase and kinase activities in mouse embryonic fibroblasts (MEFs), 25-BMC-140 (Krug) III-D-3-a/III-D-4-a- Viral and host determinants of gamma-herpesvirus pathogenesis. This registration updates and replaces registrations: RD-19-IX-07, RD-19-IX-08, RD-19-IX-09, 7707, 7708, and 7709 previously reviewed and approved by the NIH IBC, 25-BMC-141 (Love) III-E-3 NICHD Transgenic Core (general non-vectored gene editing approach), 25-BMC-142 (Ziegelbauer) III-E-1- Identifying targets and functions of viral microRNAs. This registration updates and replaces the following registrations: RD-09-VI-11 and 5017, 25-BMC-143 (Love) III-E-3/ III-D-4-a- Ribonuclease H Mutants. This registration updates and replaces previously approved 24-BMC-061 describing work under III-D-4-a and III-E-3. (PI Crouch), 25-BMC-145 (Burgess) III-E-1/III-D-4-a- Zebrafish Transgenic Core. This registration updates and

replaces previously approved registrations RD-17-VII-07 and RD-17-VII-08, 25-BMC-146 (Prokunina) III-E-1- In vitro application of multiple new recombinant plasmids, 25-BMC-147 (Miwa) III-E-1- Methods in Molecular Biology and Immunology Training (recombinant protein expression in human cells), 25-BMC-148 (De Ravin) III-C-1- Lentiviral Gene Transfer for Treatment of Children Older than 2 Years of Age with X-Linked Severe Combined Immunodeficiency. Administrative replacement-registration updates and replaces registration RD-09-II-07, 25-BMC-150 (Aladjem) III-D-3-a- Regulation of expression of protein of interest using lentiviral systems. Administrative replacement- registration updates and replaces registrations: RD-17-X-13, PRD 7437, and PRD 7244, 25-BMC-152 (Wiestner) III-E-1- Genetic mutations in the development of drug resistance in human chronic lymphocytic leukemia and other cancers, 25-BMC-155 (Cheng) III-E-1/III-D-3-a- BSL-2 Registration for the Functional Genomics Laboratory at NCATS (Core). All recombinants involving viral vectors will be described in separate registrations provided by the submitting PI responsible for each project to the Core, 25-BMC-156 (Lee) III-E-1- In-vitro and 'in-cellulo' studies of G3BP (plasmid based expression), 25-BMC-158 (Yang) III-D-3-a- Transient expressing transcription factors in human T cells using recombinant Adenovirus. Administrative replacement- This registration updates and replaces registrations RD-04-II-05 and 3805.

c. Registration amendments: Approved RD amendments ('amend 250903') for the Minutes: RD-23-III-15 (amend-Cohen), RD-17-III-06 (amend-Redmond), RD-22-IX-11 (amend-Moutsopoulos), RD-19-XII-07 (amend-Otto) RD-22-IX-18 (amend-Moutsopoulos), RD-16-VIII-03 (amend-Otto), 24-BMC-075 (amend-Lifson), RD-11-XI-10 (amend-Lazerevic), RD-12-II-05 (amend-Dunbar), 25-BMC-062 (amend-Mannes), 24-BMC-237 (amend-Wu), RD-22-VIII-19 (amend-Henderson), RD-18-VIII-03 (amend-Bosselut), RD-20-IX-03 (amend-Swaroop), 24-BMC-075 (amend-Lifson), 24-BMC-017 (amend-Pierson), RD-20-I-07 (amend-Brownell), 25-BMC-002 (amend-Wiestner), RD-17-IV-06 (ConRev-Rosenberg), RD-22-XII-07 (amend-Schoenbaum), RD-19-X-09 (amend-Robey), RD-23-VI-04 (amend-Kaplan), 25-BMC-062 (amend-Mannes), RD-20-VIII-11 (amend-Adams), RD-23-IV-03 (amend-Rosenberg), 24-BMC-082 (amend-Porter), RD-23-VI-15 (amend-Chiorini), RD-16-XI-01 (amend-Hunter), RD-15-I-09 (amend-Hunter), RD-19-IX-04 (amend-Terabe), 25-BMC-012 (amend-Katzelnick), RD-20-VIII-11 (amend-Adams)

d. Committee discussion: No committee members voiced comments or concerns.

e. After providing descriptions, the BSO asked if there were any questions or concerns with the preliminary approvals. Hearing none and following the formal review and discussion at the meeting, the IBC concurs unanimously with and formally approves the registrations and registration amendments.

II. Registrations and other submissions for Committee Review

a. Clinical trial reviews

25-BMC-159, Patrick Pinto (Presented by Howard Parnes)

i. Reviewers: Billioux, Goff, All

ii. Review summary: Dr. Howard Parnes presented for Dr. Pinto who could not make the meeting. Modified Ad5 vaccine targets Brachyury, Muk-1, PSA (plus superagonist). Active surveillance is preferred for prostate cancer patients, but 1/3 will require therapy due to progression. Single arm/phase II trial, 3 separate injections administered subcutaneously as described. Included a follow up at 4 years. Discussion of endpoints was given. The Ad5 has E2b gene deletions required for viral replication, so this is non-replicating. Safety of vaccine is well documented. This study aims to determine the effect of an Ad5 PSA/MUC-1/brachyury-based immunotherapy vaccine (TriAdeno) with IL-15 superagonist N-803 on immune infiltration of the local tumor environment by comparing pre- and post-treatment CD8+ and CD4+ T-cell density within the malignant portion of prostate biopsies in participants on active surveillance for low- and intermediate risk prostate cancer.

Background information was provided through slides. The combination of the TriAdeno vaccine and N-803 has recently been studies in patients with Lynch syndrome (NCT05419011) and there are preclinical and clinical data to support a Phase II study to evaluate the efficacy and

immunogenicity of this combination in PCa. Unlike the previous studies evaluating the immune response in patients with metastatic disease, patients with early stage, localized disease have a relatively small tumor burden, suggesting less immune dysregulation caused by T-cell tolerance to tumor tissue. Indeed, memory T cells can limit the immune response based on recognition of tumor-associated antigens and often reside inside the tumor tissue. If an effective local immune response is generated in patients with localized disease, such a strategy could prevent or intercept PCa in an earlier therapeutic window before progression to advanced disease. Such an approach could complement PSA-based screening to reduce the associated harms of overtreatment with radical therapy.

Additionally, while consideration may be given to an approach utilizing a single antigen-based vaccine approach, previous data indicate that this may be insufficient to produce a robust immune response or meaningful clinical benefit. A previous trial evaluating a poxviral based vaccine with PSA as the tumor associated antigen, PROSTVAC, demonstrated no difference in CD8+ or CD4+ T-cell infiltration in biopsy tissue compared to placebo in a randomized cohort of 154 men on active surveillance. No difference in post-vaccination peripheral immune response or PSA was noted. In contrast, the Phase I trial evaluating the safety of TriAdeno in men with metastatic castrate resistant PCa demonstrated that while TAA response to each vaccine component ranged between 53-81%, when pooled a measurable TAA response to any antigen was observed in 94% of patients.

The research group therefore proposes a Phase II study of the trivalent vaccine in conjunction with N-803 to assess the efficacy in a population with lowgrade cancer undergoing active surveillance. Given the lack of a significant peripheral immune and PSA response for TriAdeno alone in the metastatic castrate-resistant population previously reported, the addition of N-803 may promote T cell and NK cell activation and induce a more robust immune response in combination with the vaccine regimen. In combination with vaccines, N-803 may boost vaccine immunogenicity and overcome the immunosuppressive tumor microenvironment.

iii. Committee discussion:
- Committee asked whether the patients have cancers, Lynch Syndrome, or if this proposed treatment is for prevention. Presenter responded that this is for patients with polyps.
- The protocol is well described, and this is a drug/ agent the Clinical Center (CC) is very familiar with so the handling of this is no issue at the CC. All biosafety precautions have been handled appropriately.

iv. Bloodborne pathogen training (BBP) for anyone handling clinical samples, and PPE as appropriate for standard precautions and as determined by risk assessment including gloves, gown, and face protection would help mitigate risks of inadvertent exposure during agent preparation and administration, especially when working outside of primary containment such as a Biological Safety Cabinet (see other protocol details in registration).

v. Animal studies proposed: N/A

vi. The committee discussed the dual-use and ePPP potential of these experiments and agreed that there were no dual-use or ePPP concerns with this clinical protocol.

vii. There were no additional public comments.

viii. The clinical protocol is approved with standard precautions as described in place for handling therapeutic agent including gown gloves and surgical mask.

ix. Relevant sections of the NIH Guidelines: III-C-1.

x. The committee unanimously approved as written.

xi. There were no conflicts of interest indicated.

25-BMC-160, Luca Giurgea

i. Reviewers: Goff, Malech, All

ii. Review summary: Tools used to test our therapeutics have been challenge studies (various viruses including H1N1, H3N2, H10N7. Allows to study research questions very specifically. In this study, 4 different H subtypes, 4 Ns from influenza, hope to develop a balanced humoral immune response. Phase I was done 1-2 years ago, very well tolerated. Intra-nasal route was able to successfully build a response to a number of types. The current study tests efficacy and safety. It does not implement any gene transfer in humans and involves the testing of vaccine containing 4 inactivated wild-type avian influenza viruses in healthy volunteers who then undergo challenge with a live H1N1 seasonal influenza virus, which is A/California/04/2009/H1N1pdm-like. This virus has been used and tested safely in numerous clinical trialsThe purpose is to further test the safety and efficacy of a novel influenza vaccine, BPL-1357. The vaccine was tested already against placebo in a phase 1 study consisting of 45 volunteers. Here, a larger group of 126 volunteers is proposed to better assess safety and immunogenicity. However, since influenza infection and disease are sporadic in the community, efficacy is often difficult to assess in the community without conducting very large trials consisting of thousands of individuals. However, efficacy can be tested in smaller numbers using a challenge model. The group plans to test the vaccine given intramuscularly and intranasally vs placebo against influenza challenge with a seasonal H1N1 virus.

Since the start of 20th century, humanity has experienced 5 waves of influenza pandemics. The large diversity of influenza viruses in animal reservoirs portends a constant risk of the next inevitable pandemic. Current influenza vaccines are designed to protect against seasonal influenza but leave individuals largely susceptible to heterosubtypic influenza viruses. The development of a new vaccine which can greatly expand the breadth of immunity to future pandemic strains would have the potential to save many lives and decrease global morbidity by a significant amount. The BPL-1357 vaccine has demonstrated protection against hetero-subtypic influenza challenge in mice and ferrets and safety in humans in a phase 1 clinical trial.

Further study is necessary to determine if BPL-1357 also provides humans with protection against seasonal influenza. The H1N1 challenge model is ideal for this next step, as it has been well-studied and was used previously to test vaccine and therapeutic interventions. While vaccine performance of the current dose and formulation of BPL-1357 is assessed, the immune correlates of protection can also be assessed and then used to further improve broadly protective and mucosal influenza vaccines.

While the purpose of the study is to attempt an infection of participants with influenza virus, multiple precautions are in place to limit transmission of the virus to healthcare and research personnel. The study is conducted in the NIH and (UTMB) Biocontainment units. These are 2 of 14 units nationwide designed to handle admission of patients infected with select agents, such as Ebola. The units have negative pressure airflow that is separate from the rest of the hospital. Personnel are trained to manage patients with such infections. In addition to standard hospital infection control measures (e.g. handwashing), personnel wear PPE while administering virus to participants and while interacting with participants until discharge. Participants are quarantined in the Special Clinical Studies Unit (SCSU) during the study, for at least 7 days after challenge, and until they have two negative PCR tests for influenza on two consecutive days. They are screened for their living situation to not cohabitate with any other individuals who may be considered high-risk for influenza for at least 2 weeks after discharge from the SCSU. Numerous measures are in place to limit transmission to healthcare/ research personnel and close contacts. Also, transmission is notoriously difficult to orchestrate in a controlled setting. The group has not observed any clear cases in our experience (from successfully infected volunteers to uninfected volunteers) and other investigators who have attempted to design trials for the explicit purpose of studying transmission have largely been unsuccessful. Staff will handle live virus with appropriate PPE as listed (surgical mask, eye protection, gown, gloves) and administer it intranasally using a syringe and atomization device.

iii. Committee Discussion:

- Slides presented have clarified exactly what the intent is, and discussion focused on the safety of the challenges. Personnel are all appropriately monitored and cared for. The SCSU is designed just for this kind of work. The unit has negative pressure with air entering the patient rooms from the adjacent rooms and common hallway, etc. SCSU staff are trained to handle respiratory viruses and viruses of higher risk group.
- The facility is very familiar to the committee members and there are no concerns regarding patient care. But there are questions about the product safety and how it is delivered.
- It's important for the PI to state in the protocol exactly how the product is being handled and formulated, which may involve uploading SOPs from the pharmacy to the registration.
- What is the SOP for handling the agent? The virus is vialed at a particular concentration and tested in the lab to ensure the right dose is used then held in a repository. Meeting is held with pharmacy to ensure they are aware of handling and information after IRB approval. The pharmacy follows established protocols for delivery. The IB for the study also describes some of these activities.
- Committee asked if the virus is back-titred after it is diluted in the pharmacy, which has been done for some studies. Another question about the discharge showed graphs about how the virus is shed to be tested by RT-PCR on naso-pharyngeal washes – these are qualitative. Participants are discharged when they have negative tests (2) on day 6 or 7. For some studies the PCR is quantified, although this has not been done in all studies. It is very rare for patients to go beyond day seven.
- Committee discussed screening against candidates from people at home who may be at risk. For instance, elderly, pregnant woman, infants, immune-compromised contacts would make them 'at risk' (as described in the clinical trial).

iv. Expected training is BBP for anyone handling clinical samples, and PPE as appropriate for standard precautions and as determined by risk assessment including gloves, gown or labcoat, and eye protection and as described and as per risk assessment (see in registration).
v. Animal studies proposed: N/A
vi. The committee discussed the dual-use and ePPP potential of these experiments and agreed that there were no dual-use or ePPP concerns with this clinical protocol.
vii. There were no additional public comments.
viii. The clinical protocol is approved with standard precautions as described in place for handling therapeutic agent.
ix. Relevant sections of the NIH Guidelines: N/A, as no recombinant work is involved, but closest relevant section is III-C-1 (for HGT work in humans)
x. The committee unanimously approved as written.
xi. The laboratorian Luz Angela Rosas recuses herself as she was a previous member of this laboratory.

25-BMC-161, Luca Giurgia

i. Reviewers: Goff, Malech, All
ii. Review summary: This is a 'rechallenge study', using low path avian H10N7 avian influenza to measure the rate of mild to moderate influenza disease (MMID) with the second challenge. Dose escalation studies showed mild symptoms. Study structure is very similar to as just described before, after screening of participants (only those from previous study are to participate), they are slotted in for a challenge study (repeat screening for respiratory viruses), assuming all testing looks good- they are inoculated for a week. This study does not implement any gene transfer in humans. This is a study to evaluate infection after second exposure to a low pathogenicity avian influenza A H10N7. Participants who have previously been challenged with H10N7 will be challenged again at a dose of 10^7 50% Tissue Culture Infective Dose (TCID50) and followed for a minimum of 9 weeks after

inoculation. This study allows us to look at human immune responses to a low pathogenicity avian influenza virus in a controlled setting to mimic what might occur during a pandemic situation.

This virus was rescued using standard reverse genetics in a certified Vero cell line. The plasmids were made by cloning the 8 viral gene segments of the wild-type A/Mallard/Ohio/99/1989 H10N7. The viral seed stock was used for Good Manufacturing Practice (GMP) manufacturing of the challenge strain in the Vero cells (IND 14969). This study involves infecting healthy volunteers with influenza virus. There are no risks of integration or expression but there are risks associated with influenza. Clinically, influenza symptoms may vary widely. Participants in our previous challenge studies either had no symptoms or mild-to-moderate symptoms. Generally, participants who have symptoms can expect typical influenza symptoms such as fever, cough, sore throat, runny nose, muscle aches, headaches, and fatigue. However, influenza can also, though rarely, cause serious life-threatening disease and complications such as pneumonia or sinus-infections. Multiple measures ensure that the risk of severe influenza manifestations is minimized. Participants undergo thorough medical screening to ensure they are as healthy as possible including with medical history, medical exam, laboratory testing, ECG, and pregnancy testing. Participants are quarantined in the SCSU biocontainment unit during the challenge study, for at least 7 days after challenge, and until they have two negative PCR tests for influenza on two consecutive days.

While the purpose of the study is to attempt an infection of participants with influenza virus, multiple precautions are in place to limit transmission of the virus to healthcare and research personnel. The study is conducted in the NIH Biocontainment unit (the Special Clinical Studies Unit). As described in the earlier protocol, the units have negative pressure airflow that is separate from the rest of the hospital and have personnel that are trained to manage patients with such infections. In addition to standard hospital infection control measures (e.g. handwashing), personnel will wear PPE while administering virus to participants and while interacting with participants until discharge. Participants are quarantined in a biocontainment unit during the challenge study, for at least 7 days after challenge, and until they have two negative PCR tests for influenza on two consecutive days. Participants are screened for their living situation, to not co-habit with any other individuals who may be considered high-risk for influenza. Staff will handle live virus with appropriate PPE as listed above (surgical mask, eye protection, gown, gloves) and administer it intranasally using a syringe and atomization device. Research personnel are trained medical personnel with expertise in influenza/infectious diseases and clinical trials, many with experience conducting influenza challenge studies. Clinical staff are trained, medical personnel, including those with specific training in managing patients with infections in biocontainment units. Clinical personnel will receive a presentation on the study by research staff, including on potential exposure risks and mitigating strategies.

iii. Committee Discussion:

- Most discussion occurred together in the context of the review of the first of these two trials.
- Intent is very clear, including the engineering controls for biosafety. SCSU unit is built to contain this, and all personnel are trained. Clinicians have great familiarity with this but are curious about pharmacy SOPs. Pharmacy representatives were previously advised by the IBC about handling different therapeutics. This was discussed and the pharmacy is advised as far as that previous communication. Who currently inspects the pharmacy is unclear in the context of clinical center operations and a longstanding safety representative has recently left the NIH. The committee seeks to ensure there is no safety gap, and the registration should reflect how the product is being safely handled. There must be an SOP in place and there was discussion about whether that should include if handlers are immunized. Dr. Giurgea mentioned after the virus is vialed, it is

tested and when ready for the study a meeting occurs where this information is shared, and it is all within the investigator's brochure.

- Committee discussed whether it would need to review this kind of protocol again if the same virus, units, and pharmacy are being used.
- The potential for DURC was discussed and the committee had absolutely no comments or concerns in this regard for all the clinical trials discussed. Community members commented on the serious degree in which the IBC does its business and was grateful for such oversight.

iv. Expected training is BBP for anyone handling clinical samples, and PPE as appropriate for standard precautions and as determined by risk assessment including gloves, gown or labcoat, and eye protection and as described (see in registration).
v. Animal studies proposed: N/A
vi. The committee discussed the dual-use and ePPP potential of these experiments and agreed that there were no dual-use or ePPP concerns with this clinical protocol.
vii. There were no additional public comments.
viii. The clinical protocol is approved with standard precautions as described in place for handling therapeutic agent.
ix. Relevant sections of the NIH Guidelines: N/A, as no recombinant work is involved, but closest relevant section is III-C-1(for HGT work in humans)
x. The committee unanimously approved the clinical trial as written with precautions described.
xi. The laboratorian Luz Angela Rosas recuses herself as this was her previous laboratory.

b. Special reviews

PRD 8718 amend 250903, Bernard Moss

i. Reviewers: Craigie, Whithead, All
ii. Review summary: The NIAID investigators would like to receive serum (inactivated by heating) from MPXV infected NHPs for analysis of antibodies that bind to viral proteins. Serum is diluted in FBS, 1mL into tubes and triplicated then sealed and heated at temperature for time points, then plates onto monolayers for growth, then aspirated, then incubated- all as described. 60° and 65°Celsius (65°C) was tested for 5, 10, 15, 20 and 30 minutes). Inactivation of Vaccinia virus was proposed as a surrogate for the MPXV. Inactivation methodology was discussed. Results are tabulated. The specifics were given and discussed. Plan is to inactivate at 65°C for 20 minutes which seems fine for the vaccinia virus and builds in an additional safety factor of 5 minutes as shown in the data.
iii. Committee Discussion: the registration amendment wording language needs to be corrected prior to approval- as they are proposing here 65 degrees Celsius for 20 minutes. Regarding surrogate usage- the IBC has and does approve surrogates so long as the representative agent is in the same family.
iv. Training on the SOP should be given so all laboratory personnel are aware of the SOP. PPE requirements are consistent with regular laboratory requirements for this level.
v. Animal studies proposed: No animal work was discussed in context of this amendment.
vi. The committee discussed the dual-use and ePPP potential of these experiments. The committee agreed that there were no dual-use or ePPP concerns with the proposed amendment.
vii. There were no additional public comments.
viii. Work is approved at: Inactivation parameters of 65 degrees Celsius for 20 minutes were approved for work with the samples at BSL-2.
ix. Relevant sections of the NIH Guidelines: Not applicable; no recombinant work in this amendment
x. The committee unanimously approved as written.
xi. There were no conflicts of interest indicated.

25-BMC-162, Michael Holbrook

i. Reviewers: Billioux, Whitehead, All

ii. Review summary: This registration updates and replaces the following registrations: Yellow fever virus (YFV, under 5796), West Nile virus (WNV, under 5797), Powassan virus (POWV, under 5798) and Japanese encephalitis virus (JEV, under 8962).

- This registration is an administrative replacement with no significant changes from prior approval. This is an administrative approval, no new work has been submitted, reviewed, or approved in this initial submission. Work under the consolidated PRD will initially focus on cell-based assays and experiments. Any animal work will be added by amendment. The objective of this project is to experimentally define cellular responses to flavivirus infection that are related to differential aspects of virus infection. This effort will focus on neurotropic mosquito (JEV and WNV) and tick-borne (POWV, strain LB) viruses as well as a highly pathogenic viscerotropic (YFV) flavivirus. Additional work under this PRD will include comparative studies with related attenuated vaccine isolates (managed under a separate PRD) to help identify specific cellular responses related to vaccine virus attenuation. There is no TBEV vaccine in the US.

- Work as described with YFV and JEV is approved using BSL-3 level practices and procedures. Personnel must follow the SOP for entry and exit procedures. All personnel working in this space must be cleared by the Division of Safety and the Biosurety program prior to entry. Agent specific training by the PI must precede personnel entry. Work as described with Powassan virus is approved at the established BSL-2, with certain BSL-3 practices (BSL-2/3). (*Chiefly BSL-2/3 calls for enhanced practices in a BSL-2 facility: (1) fastidious adherence to proper microbiological techniques, (2) decontaminating all potentially infectious waste, (3) working in a BSC wearing proper PPE- double gloves, eye and mucus membrane protection, tie-back gown, (4) use of gasketed safety cups for centrifugation procedures, and (5) minimizing the use of sharps, among other considerations to minimize worker exposure to aerosols, such as only working in a certified Class II BSC for any procedures that may generate aerosols*). Work as described with West Nile Virus is approved at BSL-2. A 1-2-3 poster must be displayed in the laboratory and all personnel on this.
- registration must maintain annual lab safety through the Division of Safety. Care should be taken to minimize worker exposure to aerosols, such as working in a certified Class II BSC and using gasketed bucket covers when centrifuging.

iii. Committee Discussion: Any stock of West Nile Virus that is already in BSL-3 containment must be worked with at BSL-3 level practices and

iv. No recombinant or animal work is submitted, reviewed or approved in this registration.

- Many JEV strains are listed. There is a JEV vaccine recommended prior to work. For WNV it is a BSL-2. YFV vaccination is highly recommended (8 different strains listed).
- In latest edition of BMBL- Powassan virus is at BSL-3. All strains are in the BSL-3 or BSL-4 freezers.
- Also recommend WNV remain at BSL-3, they do not have a BSL-2 strain derived outside of BSL-3.
- If all work is proposed to be at BSL-4 for their purposes, it will remain at that.
- For any containment-lowering requests, there are practices the IBCs have discussed and agreed on and all work with agents will remain at their approved level until they submit data and requests for lowering.
- BSOs have discussed with the laboratory procedures on how to resubmit work to the IBC for clarity when consolidating registrations.

v. Expected training is BBP for anyone handling human cells or materials, and appropriate training per the BSL for the high containment laboratories. A 1-2-3 poster must be displayed in the laboratory and all personnel on this registration must maintain annual lab safety through the Division of Safety. PPE as established for these laboratories and locations (see in registration).

vi. Animal studies proposed: None.
vii. The committee discussed the dual-use and ePPP potential of these experiments and agreed that there were no dual-use or ePPP concerns with this clinical protocol.
viii. There were no additional public comments.
ix. The registration was unanimously approved at the biosafety levels described during review for the agents discussed and as written above.
x. Relevant sections of the NIH Guidelines: This does not apply, IBC review for work with high containment pathogens.
xi. The committee unanimously approved as written.
xii. There were no conflicts of interest indicated.

25-BMC-163, Ursula Buchholz

i. Reviewers: Whitehead, Denny, All
ii. Review summary: The NIAID investigators a fusion between two labs- this is going to go on Dr. Buchholz's LID-34E. This is a reassortant chimeric virus being proposed to be handled at BSL-3. The laboratory is developing live parainfluenza virus-based vector vaccine candidates for intranasal immunization against avian influenza virus (designed and evaluated under separate registrations). They have developed live-attenuated parainfluenza virus type 3 (PIV3; based on bovine/human PIV3; B/HPIV3) vaccine candidates expressing H7N9 antigens of avian influenza virus (AIV) (A/Guangdong/17SF003/2016) from added genes (RD-16-II-05, recombinant parainfluenza virus vaccine candidates). These were designed as bivalent parainfluenza virus 3/influenza virus vaccine candidates for intranasal immunization. The group is planning to test their efficacy in the hamster model. Hamsters will be immunized intranasally with our vectored vaccines (covered by separate registrations). Vaccine efficacy will be evaluated by intranasal challenge with a reassortant influenza vaccine virus bearing the internal genes of mouse-adapted A/Puerto/Rico/8/34 (PR8), with the H7 and N9 genes derived from avian influenza virus (Guongdong strain) which was developed by the Taubenberger laboratory, and the proposed animal work is covered by this registration. This challenge virus corresponds to the H7N9 vaccine virus in the national stockpile. It is attenuated by the PR8 backbone. The challenge will be performed in collaboration with Drs. Taubenberger and Kash, Viral Pathogenesis and Evolution Section. All subsequent laboratory work will be performed under their registrations. This registration document covers the animal study component, i.e., a hamster challenge that will be performed by our laboratory staff under my ASP, LID 34E, in Building 33 (ABSL3, suite BW01L). For clarification, the reviewer identified where the tissues will be going after they are collected in the BSL-3 facility, and it is confirmed this will be to the Taubenberger laboratory at BSL-3. This should be clarified (written) in the registration itself. (same building and laboratory safety level).
iii. Committee Discussion: Animal work is approved at BSL-3. The tissues going to the BSL-3 laboratory are transferred within the same building. The proposal was discussed between both reviewers and both agreed on the findings and that the ASP was appropriately described.
iv. Training in addition to regular requirements including ABSL-3 and proficiency training. PPE requirements should be consistent with regular laboratory requirements for this level.
v. Animal studies proposed: Yes, hamsters.
vi. The committee discussed the dual-use and ePPP potential of these experiments. The committee agreed that there were no dual-use or ePPP concerns with the proposed amendment.
vii. There were no additional public comments.
viii. Work is approved at: Animal work at ABSL-3 practices and containment.
ix. Relevant sections of the NIH Guidelines: III-D-7 for experiments with influenza viruses generated by recombinant or synthetic methods.
x. The committee unanimously approved as written.
xi. There were no conflicts of interest indicated.

c. Registrations for committee review

25-BMC-164, Mark Connors

i. Reviewers: Craigie, Billioux

ii. Review summary: This NIAID study will use vesicular stomatitis virus (VSV) as a vaccine vector for HIV but may be extended to other pathogens in the future. The laboratory recently published that CD8+ T cell avidity is a critical parameter associated with immunologic control of HIV in vaccinated individuals (Migueles et al. Science, 2023). In that paper the only vaccinees that developed high avidity responses were those that received 3 injections of a DNA vector followed by a VSV vector. It is likely that replicating VSV drove clonal selection of T cells in a manner that other non-replicating vaccines did not. In this project they are comparing the B cell and T cell response in macaques to replicating and non-replicating VSV vectors. The animal work will be performed by our collaborator, Dr. Paolo Lusso. Propagation in E. coli of VSV vectors expressing Lassa GP and HIV env, gag, and VSV structural gene. This is a non-integrating virus. For eukaryotic work plasmids will be transfected int Hela cells and the resultant viruses purified, proposed at BSL-2/3, animal work to be carried out by the collaborator. In this case, expression isn't a risk to workers. The virus can infect workers but is unlikely to cause disease except in those that are severely immunosuppressed.

iii. Committee Discussion: There was a question as to whether prokaryotic work was proposed, because of the stated work with lab strain E. coli; the stated level is appropriate. There are no DURC related issues.

iv. Training and PPE requirements as established with BSL to be in line with a BSL-2 laboratory, to include laboratory safety training and BBP training for individuals handling any human materials. PPE standards include protective labcoat, gloves and eyewear.

v. Animal studies proposed: Not described here as this is done by collaborator.

vi. The committee discussed the dual-use and ePPP potential of these experiments. All answers were ‘no’ and investigators will be asked to confirm with the BSOs. The committee agreed that there were no dual-use or ePPP concerns with the proposal so long as no GOF experiments were being performed.

vii. There were no additional public comments.

viii. Work is approved at: Prokaryotic work is approved at BSL-1, eukaryotic work is approved at BSL-2/3. No animal work is proposed by this investigator.

ix. Relevant sections of the NIH Guidelines: Prokaryotic work is at III-D-2-a, eukaryotic work is approved under III-D-3-a.

x. The committee unanimously approved with minor modifications and clarifications as discussed.

xi. There were no conflicts of interest identified.

25-BMC-165, Linehan

i. Reviewers: Denny, Goff

ii. Review summary: The NCI investigators wish to modify a human renal cancer cell line (EOK124) established from a TFE3-fusion kidney cancer surgically removed from a patient managed at the Urologic Oncology Branch. UOK124 cell line established from TFE3-fusion kidney cancer is tumorigenic in immunocompromised mice. The group has in vitro evidence suggesting that inactivation of the WDR24 gene will impact the tumorigenic properties of this cell line. They plan to inactivate the WDR24 gene in the UOK124 cell line using CRISPR/cas9 gene editing technology and then compare its tumorigenic properties with the parent UOK124 line in mice. Mouse work is covered in ACUC approved ASP PB-029-4. Not able to open it. WDR24 is a member of the GATOR2 complex localized on the lysosomal surface which activates TORC1 by opposing the function of TORC1 inhibitor GATOR1. Recent evidence for an mTORC1- independent pathway supports that the GATOR2 complex protects TFE3, driver of lysosome biogenesis, from proteasomal degradation. The group hypothesizes that WDR24 inactivation by gene editing will result in loss of TFE-fusion transcriptional activity and result in tumor growth inhibition in the xenograft model. Transfecting cells as described and knocking

out the WDR24 gene. No viral vectors will be used to alter the cell lines. Animal work will involve immunocompromised mice.

iii. Committee Discussion: One of the attachments may not apply. No additional discussion after review. Check on the unusual attachment.

iv. Training and PPE requirements as established with the ABSL-2 level, to include laboratory safety training and animal training requirements per OACU.

v. Animal studies proposed: Yes, mice

vi. There were no dual-use and ePPP potential of these experiments. The committee agreed that there were no dual-use or ePPP concerns with the proposal.

vii. There were no additional public comments.

viii. Work is approved at: Eukaryotic work at BSL-2. Animal work at ABSL-2 practices and containment

ix. Relevant sections of the NIH Guidelines: III-D-3- a for eukaryotic work. Animal work at III-D-4-a, ABSL-2→1 after injection (with no weeping) and housing at ABSL-1.

x. The committee unanimously approved as written.

xi. No conflicts of interest were identified.

25-BMC-166, Lupica

i. Reviewers: Denny, Whitehead

ii. Review summary: The NCI investigators plan to investigate addictive behaviors using adeno-associated virus (AAV) vectors in rats. Studying impacts of THC using various AAV vectors. Behavioral and electrophysiological recordings are taken from brain slices from animals they could not train or others.

The overall goal of this study is to examine the role of the lateral habenula (Lhb) and its role in behavior. The laboratory has previously found an important role for this brain area in impulsivity, which is a key hallmark of addictive behaviors. Here they will study the activity of nerve cells (neurons) in the LHb in an animal model where rats learn to press a lever to receive a food reward. They will monitor the activity of LHb neurons using a technique known as fiber photometry. In this technique, a fluorescent protein is expressed in the brain, and a small fiber detects light emitted from the protein whenever the protein is activated. They use this to track the activity of LHb neurons, as well as the release of chemical substances in the LHb. They propose to use these approaches in both control rats, and in rats that have been exposed to THC, the primary active ingredient in marijuana. These studies will help to inform us of changes that occur in this important brain area following exposure to this widely abused drug. Eight different AAVs will be used as described. All rAAVs are purchased and ready to inject. (Optigenic activation).

In the proposed studies, they will use several approaches to examine the LHb. First, is to use thin slices of brain tissue (brain slices) from rats to measure the electrical activity of LHb nerve cells and examine how this activity changes after rats are exposed to THC. Second, they can measure LHb nerve cell activity and acetylcholine release in awake, behaving rats that are trained to press a lever for food or are exposed to mild stress. They do this using a technique known as fiber photometry, in which a small fiber can detect brain activity by measuring light produced by proteins ('fluorescent proteins') that are injected into the brain. They then see how LHb neurons are active and how acetylcholine is released under normal conditions and following exposure to THC. Using these approaches, they hope to better understand the function of the LHb during behavior, and how exposure to THC changes this important brain area. References were included.

iii. Committee Discussion. Proposal was very thoroughly reviewed as warranted. Dr. Whitehead had no additional comments.

iv. Training as standard including Laboratory Safety Training and BBP training for individuals working with human materials (as applicable).
v. Animal studies proposed: Yes, rat
vi. The committee discussed the dual-use and ePPP potential of these experiments. The committee agreed that there were no dual-use or ePPP concerns with the proposal. All answers were “no.”
vii. No additional public comments were given.
viii. No prokaryotic or eukaryotic work is described. Animal work is approved at ABSL-1.
ix. Relevant sections of the NIH Guidelines: Animal work at III-D-4-a
x. The committee unanimously approved this protocol only after additional information is given as described.
xi. No conflicts of interest were identified.

25-BMC-167, Williamson

i. Reviewers: Billioux, Craigie
ii. Review summary: The NIAID investigators want to perform a “photo activatable, ribbonucleoside enhanced cross linking and immuno precipitation”- ‘Par-clip’ experiment on an RNA binding protein Ddx6 (‘Deadbox helicase6). High amount of protein is needed for a successful immuno-precipitation. Therefore, a DDX6 overexpression cell line was made in a Jurkat cell line (ATCC E6-1) by using lentiviral transduction method. This experiment will be used to identify any RNAs that bind to the DDX6 protein by using an immunoprecipitation with Anti-Ddx6 antibody followed by RNA extraction and RNA sequencing. The enriched RNA fragments will help us identify RNA binding partners with Ddx6 and facilitate the further mechanism study of the role of DDX6 in RNA regulation. Ddx6 has been reported to play an important role in mammalian decapping complex, mRNA splicing and mRNA shuttling between cytoplasm and stress granules or P-bodies. This gene's dysfunction has been associated with cancer development, virus infection, neuron degeneration and autoimmune diseases. In our on-going research study, Ddx6 appeared to regulate the FOXP3 mRNA expression at the posttranscriptional level by either mediating the mRNA decay or by repressing protein translation. A specific MicroRNA (mir1246) was also found important for this inhibition process. To further explore if the Ddx6 protein can directly bind to FOXP3 mRNA or its associated miRNAs, the Par-clip method is a useful tool to investigate this hypothesis. Creating an oncogenic risk for humans. DURC question 6 (enhanced susceptibility to the host population) is erroneously answered yes, not appropriate because they are only knocking out a gene. Most maps are provided, but a few maps need to be provided.
iii. Committee Discussion: Their ddx6 plasmids are attached with descriptions and looks like a fourth or third generation system. The secondary reviewer had no other comments.
iv. Training and PPE requirements as established with BSL-2, to include laboratory safety training, and minimal PPE requirements including protective lab coat and eyewear.
v. Animal studies proposed: No.
vi. The committee discussed and agreed that there were no dual-use or ePPP concerns with the proposal.
vii. No additional public comments were made.
viii. Work is approved at: No prokaryotic work is being proposed. Eukaryotic work at BSL-2.
ix. Relevant sections of the NIH Guidelines: Eukaryotic work at III-D-3-a using in house established system with 293T.
x. The committee unanimously approved as written.
xi. No conflicts of interest were identified.

25-BMC-168, Muthuswamy

i. Reviewers: Goff, Denny

ii. Review summary: Review was a bit confusing as some documents were mixed with those pertinent to the review of the amendment from the same PI. Goal is to study cell polarity in cell organoids in cancer tissue samples. They have been receiving tissue samples and now want to use RV and LV to do cDNA work to start evaluating tissues. The laboratory has expertise in developing and utilizing cancer models and have been at the forefront of exploring the cellular and biological mechanisms that regulate cancer progression and treatment resistance. Also perform translational research opportunities to define how cancer cells repurpose polarity proteins to develop resistance to therapies while challenging the notion that polarity proteins function solely as tumor suppressors. Prokaryotic work and eukaryotic (cancer cells) will be performed at BSL-2. They discussed using a second-generation LV packaging system which will be BSL-2/3.

One problem is that cancer patients, including those with breast and pancreatic cancer, undergo a variety of treatments, including but not limited to radiotherapy, chemotherapy, molecularly targeted therapies, and immunotherapies. Regardless of the stage and location of the disease within a patient, the development of resistance to these treatment modalities is arguably the most critical factor contributing to the fatality of patients. Therefore, preventing or overcoming treatment resistance is a critical unmet need for controlling cancer and reducing mortality. To shorten the knowledge gap, recent advances in cancer genetics, epigenetics, single-cell and spatial genomics, and various omics approaches have improved our understanding of the genetic, epigenetic, and signal transduction mechanisms associated with therapy resistance. However, the role of cell biological processes, such as cell polarity, intracellular protein trafficking, and cellular metabolism, in regulating therapy resistance remains poorly understood. Thus, this is an underexplored research area that presents new opportunities for therapeutic development. Using lentiviral and retroviral vectors, cDNA will be expressed for genes that can potentially regulate resistance to drugs and immunotherapies to identify new regulators of resistance.

iii. Committee Discussion. Dr. Denny had questions about some of the agents and the appropriate biosafety level for the animal experiments. The agents are administered through intra-cerebral injections, which could be performed using ABSL-2 for injection followed by ABSL-1 housing. With primates it may stay at ABSL-2 or could be considered ABSL-1 with NIH 3044-2, ferrets can be housed down to ABSL-1 after intra-cerebral injection.

iv. Training and PPE requirements as established, including LST and BBP training. Animal training for ABSL-2 work as outlined by OACU.

v. Animal studies proposed: Yes, NHPs and ferrets

vi. The committee discussed the dual-use and ePPP potential of these experiments. The committee agreed that there were no dual-use or ePPP concerns with the proposal.

vii. No additional public comments were received.

viii. Work is approved at: Prokaryotic work is proposed at BSL-2, and this is fine, eukaryotic work is approved at BSL-2/3, Animal work is approved at ABSL-2 at injection, followed by ABSL-1 housing with NIH MC 3044-2 for working with NHP.

ix. Relevant sections of the NIH Guidelines: Animal work is approved under section III-D-4-a

x. The committee unanimously approved as written.

xi. No conflicts of interest were identified.

25-BMC-169, Cheng

i. Reviewers: Craigie, Denny

ii. Review summary: The investigators found that Glypican-1 (GPC1) is upregulated in anaplastic thyroid cancer (ATC) compared to papillary thyroid cancer (PTC). The group will evaluate whether GPC1 is an effective therapeutic target for treating ATC. No prokaryotic work, eukaryotic work will involve ATDD cell lines. Recently, the group identified that GPC1 is upregulated in ATC tumors. In this proposal, the group will evaluate whether GPC1 CAR-T cells can be effective in treating ATC. GPC-1 knockout lines will also be evaluated. Goal of animal work is to determine if

these experiments can extend mice survival under conditions. Range of dose is given and seems prudent. Secondary reviewer notes agree with the assessment.

iii. Committee Discussion: No additional discussion after review.

iv. Training and PPE requirements: laboratory safety training and BBP training for individuals working with human cell lines.

v. Animal studies proposed: Yes, mice

vi. The committee discussed the dual-use and ePPP potential of these experiments. The committee agreed that there were no dual-use or ePPP concerns with the proposal.

vii. There were no additional public comments.

viii. Work is approved at: Eukaryotic work will be approved at BSL-2, animal work at ABSL-2.

ix. Relevant sections of the NIH Guidelines: Eukaryotic work at III-D-3-a, Animal work at III-D-4-a.

x. The committee unanimously approved the proposal as written.

xi. There were no conflicts of interest identified.

25-BMC-170 Douek

i. Reviewers: Denny, Whitehead

ii. Review summary: Under this protocol, they aim to immunize NHPs via a prime-boost strategy using RABV, MOKV, IKOV, EBLV-2 mRNA-LNP vaccines to obtain virus-specific antigen immune blood. They would like to: (1) isolate and characterize neutralizing antibodies to RABV, MOKV, IKOV in NHPs. (2) determine if a heterologous boost with the same phylogroup (RABV followed EBLV-2) or different phylogroups (RABV followed by MOKV, or IKOV) increases the breadth of the antibody response in NHPs against divergent lyssaviruses.

Lyssaviruses genomes encode five proteins arranged in a conserved order. Of these five proteins, the glycoprotein (GPC) has been shown to be a good target for neutralizing antibodies in novel RABV mRNA vaccine studies4-6. This is because the GPC is the only exposed protein on the virion and is responsible for host cell entry7. In 2021, a clinical trial using RABV GPC lipid nanoparticle (mRNALNP) (NCT03713086) in humans, elicited neutralizing antibodies that were detected up to Day 57 in participants4. Therefore, we designed GPC mRNA-LNP vaccines for RABV, MOKV, IKOV and EBLV-2 to generate neutralizing antibodies. The full-length GPC amino acid sequence from RABV (ACR39382.1) was codon optimized for expression in NHPs and cloned into a DNA plasmid which was then used for mRNA synthesis of the full-length expression construct, including 5' UTR, 3' UTR and poly(A) tail. The mRNA was encapsulated into liponanoparticles with the SM102 formulation by Genscript. In addition to the RABV virus, mRNA immunogens were similarly prepared for MOKV GPC (AAB26292.1), IKOV GPC (AFQ62097.1), and EBLV-2 GPC (ABO65251.1). No gene-drive organisms were used or created.

iii. Committee Discussion: No additional discussion after review.

iv. Training and PPE requirements: laboratory safety training and BBP training for individuals working with human cell lines.

v. Animal studies proposed: Yes, NHPs

vi. The committee discussed the dual-use and ePPP potential of these experiments. The committee agreed that there were no dual-use or ePPP concerns with the proposal.

vii. There were no additional public comments.

viii. Eukaryotic work is approved at BSL-2, animal work at ABSL-2.

ix. Relevant sections of the NIH Guidelines: III-D-3-a and BSL-2 with containment centrifuge. Animal work at III-D-4-a for animal work at ABSL-2 practices and containment.

x. The committee unanimously approved with minor modifications.

xi. There were no conflicts of interest identified.

d. Registration amendments for committee review

RD-23-I-11 amend 250903, De Ravin

i. Reviewers: Goff, Billioux (Dr Cragie serves as chair for this review, as Dr. Malech recuses himself)
ii. Review Summary: They wish to include the hematopoietic stem cells from this patient. Amendment to include T cells. These are autologous T cells that are edited with the same editing components (all RNA) used to edit the hematopoietic stem cells (approved in original RD). Methods are all the same; it's just the material into which they are editing has changed. From a biosafety standpoint there is no difference, in fact the STEM cells have more biosafety concerns/issue than the autologous T-cells, therefore this seems fine. Hopefully the T-cells will start to take hold which takes months.
iii. Committee Discussion. Dr. Malech, who is head of the group, contributed that there appears to be something missing regarding the CD40 ligand protocol. Some pieces came from the single patient- CD40 ligand protocol and perhaps something is mixed up here. Dr. Goff indicated that the correct part is apparent in the Jan25 amend (when the CD40 ligand was added) since there was a defect in T-cells they decided to include those. Bits and pieces from the CGD document are not relevant here, its only base editing for this patient. The Jan amendment was made to this RD, instead of giving the single patient their own RD. This is a different IND, however in this case it was added as an amendment to the original protocol- and therefore it does all make sense it's just unusual to see the documents in this context. It all is rather straightforward and reviewer agreed.
iv. Training and PPE requirements are already established using standard precautions.
v. Animal studies proposed: No.
vi. The committee discussed the dual-use and ePPP potential of these experiments. The committee agreed that they felt were no dual-use or ePPP concerns with the proposal, but to be cautious they will advance the proposal for consideration by the NIH ICDUR for determination as to whether the DURC-IRE should review it.
vii. No additional public comments were received.
viii. Work is approved at: Eukaryotic work is established at BSL-2.
ix. Relevant sections of the NIH Guidelines: Eukaryotic work at III-D-3-a.
x. The committee unanimously approved as written pending and dependent on the review of the proposal by the NIH ICDUR and if determined, the NIH DURC-IRE.
xi. Dr. Malech recused himself for this review.

RD-24-II-22 amend 250903, Douek

i. Reviewers: Whitehead, Denny
ii. Review Summary: The investigators were previously approved for Spike ferritin nanoparticle (SpFN) work from specific coronavirus strains (HKU5); now proposing mRNA lipid nanoparticles (LNPs) from HKU5 and extending to the mink and the bat coronaviruses. They don't say they are using spike proteins other than SKU5 (like HKU5); this is presumed. These additional spikes are of concern of course because they use the Ace2 receptor for binding to cells. Separate particles will be made for the mink and the bat particles- 3 doses, etc. as described and they will evaluate the B-cells.
iii. Committee Discussion. No additional comments and Dr. Denny agreed it was straightforward.
iv. Training and PPE requirements as established.
v. Animal studies proposed: Yes, NHPs.
vi. The committee discussed the dual-use and ePPP potential of these experiments. The committee agreed that there were no dual-use or ePPP concerns with the proposal.
vii. No public comments were made.
viii. Animal work is approved at the established level of ABSL-2 practices and containment and following the standard procedures for working with NHP as established in NIH MC 3044-2.
ix. Relevant sections of the NIH Guidelines: Animal work at III-D-4-a
x. The committee unanimously approved as written.

xi. No conflicts of interest were identified.

24-BMC-099 amend 250903, Muthuswamy

i. Reviewers: Craigie, Goff
ii. Review Summary: The original rDNA registration for in vivo selection did not describe recombinant work, here they are adding work with lentivirally transduced cells. They have identified RACGAP1. The group would like to expand our study using pancreatic tumor models to include the Mia PaCa2 human cell line. The group proposes this experiment because RACGAP1 has been identified as a potential gemcitabine (standard of care) sensitizer in pancreatic cancer cells. High expression of RACGAP1 correlates with both poor overall survival and progression-free survival. Our goal is to examine whether Mia PaCa2 with RACGAP1 overexpression can lead to increased gemcitabine resistance in vivo. The cell line already exists but if they need to make it, BSL-2/3 will apply based on the lentiviral system they mention. Reviewer agreed this is fine and reasonable.
iii. Committee Discussion. No additional discussion other than to ensure the items and documents to clarify this with the other document previously reviewed.
iv. PPE and training requirements as established and to include BBP training for individuals handling human materials.
v. Animal studies proposed: Nothing additional here.
vi. The committee discussed the dual-use and ePPP potential of these experiments. The committee agreed that there were no dual-use or ePPP concerns with the proposal.
vii. No public comments were made.
viii. Work is approved at: Eukaryotic work at BSL-2, the work with this lentiviral packaging system will include BSL-2 with level 3 practices.
ix. Relevant sections of the NIH Guidelines: Eukaryotic work is established at III-D-3-a
x. The committee unanimously approved the registration with minor corrections as mentioned.
xi. No conflicts of interest were identified.

RD-20-II-13 amend 250903, Jiang

i. Reviewers: Denny, Craigie
ii. Review Summary: Previously approved for lentiviral transduced cells injected into mice, now wish to directly administer LNP plasmids expressing A0AH (mRNA) and therefore they need to add a new mouse procedure: Hydrodynamic tail vein injection (HDTVi), which involves tail vein injections of a few DNA plasmids into mice. The purpose of HDTVi is to trigger orthotopic liver tumors without surgery, such that HDTVi can provide a much simpler procedure than orthotopic implantation of liver cancer cell lines. The group proposes to register 6 new plasmids, including PKT2 /CLP-Vector, PKT2/CLP-Aoah, pT3-EF1a-MYC-IRES-luciferase (MYC-Luc), pT3-EF1a-MYC-IRES-luciferase-OS (MYC-LucOS), and pT3-N90-CTNNB1.

Despite the breakthrough of immune checkpoint blockade in anticancer treatment, the current immunotherapy is only effective in a minor population of patients. Through analyzing genomics data from immunotherapy clinical trials, several genes have been identified whose tumor expression levels are consistently associated with favorable or adverse outcomes. Encouraged by the evidence from human clinical data, the group set out to validate their knockout phenotype in murine models using several murine cell lines modified by CRISPR knockout or gene overexpression.
iii. Committee Discussion: No questions or additional discussion.
iv. PPE and training requirements as established.
v. Animal studies proposed: Yes. mice
vi. The committee discussed the dual-use and ePPP potential of these experiments. The committee agreed that there were no dual-use or ePPP concerns with the proposal.

vii. No public comments were made.
viii. Prokaryotic work is approved at BSL-1. No eukaryotic work. Animal work is approved at ABSL-1 containment and practices.
ix. Relevant sections of the NIH Guidelines: prokaryotic work is approved under III-D-02-a, animal work at III-D-4-a
x. The committee unanimously approved with minor modifications.
xi. No conflicts of interest were identified.

RD-23-IV-09 amend 250903, Dekker

i. Reviewers: Billioux, Craigie
ii. Review Summary: Previously approved for using a plasmid coding for SacB into a patient isolate of Burkholderia vietnamiensis - Now proposing to use the same plasmid to restore 2 wildtype genes that have mutated and inactivated themselves over the course of studying the isolates. The isolates evolved over a 5-month period that modified the analysis.

NIH has been studying a set of Burkholderia vietnamiensis isolates cultured from a single NIH Clinical Center patient. These isolates evolved over a period of 5 months during infection of the patient and acquired genetic changes that modulated the behavior of the intrinsic stringent/starvation response, involving the spoT and relA genes. The native spoT gene was inactivated through an ancestral IS element insertion and subsequent disrupting mutations occurred within the relA gene. As noted above, these two genes regulate the stringent/starvation response, and the group hypothesizes that inactivation of these two genes may have been a positively selected adaptive change that occurred during the infection.

In this Amendment, the group proposes to study how the spoT and relA genes contribute to the stringent/ starvation response in this isolate set, and how the inactivation that occurred during the infection may have modulated starvation response biology. This will be done by in trans (non-integrating plasmid based) complementation of the inactivated genes with the wild type spoT and relA genes, along with introduction of an RNA-based sensor that will produce a fluorescent read-out of the concentration of (p)ppGpp, a key metabolite produced during the starvation response that can be used as a reporter. The group also proposes to introduce fluorescent labeling on a non-integrating plasmid.

Kanamycin and Chloramphenicol are the two antibiotic resistance genes that are used as selection markers, and these represent two antibiotics that are not used (or available) in the U.S. for human clinical care. Plasmid details are given and marker genes discussed. Vectors generated by GeneWiz. The DURC question for these antibiotics does not make it of concern.

iii. Committee Discussion: Dr Craigie had nothing to add.
iv. PPE and training requirements as established.
v. Animal studies proposed: No
vi. The committee discussed the dual-use and ePPP potential of these experiments. The committee agreed that there were no dual-use or ePPP concerns with the proposal. They are using typical antibiotic marker selection which adds no issues pertaining to DURC.
vii. No public comments were made.
viii. Work is approved at: Prokaryotic work approved as proposed BSL-2, no additional eukaryotic work over what is already approved.
ix. Relevant sections of the NIH Guidelines: Prokaryotic work will be done, at III-D-1-a and BSL-2.
x. The committee unanimously approved with minor modifications.
xi. No conflicts of interest were identified.

III. Committee Review of Inactivation Procedures: None other than as reviewed in the #6718 amendment.

IV. Standard Operating Procedures/Plans: None

V. Serious Adverse Events in Clinical Trials reviewed by the Committee: None

Reports

I. Biosafety Officer Report will be electronically sent for committee review. In June and July 2025, there were 28 research-related incidents: None involved work with rDNA, 10 sharps-related incidents, 11 related to work with NHPs (6 direct and 5 associated with work with NHP), 13 involving research with other animals (mostly rodent bites), 2 related to potential exposures to HBBF for research related incidents (not related to patient care), and 1 involved potential exposure to "other" human pathogens.

The BSO reminded everyone he has reviewed the preliminarily approved registrations and registration amendments and asked again if there were any other concerns or questions about those approvals. In the absence of any further comments, these registrations and registration amendments are formally approved.

Other reports: None

Around the Room/Committee Discussion

- Another reminder: as of June 2025, the OSP has mandated all IBC minutes will be publicly posted in a streamlined format. The four NIH IBCs have agreed on and are using the new template and it is expected that IBC members must recuse themselves from discussions where they have conflicts of interest (as they have always done).
- Dr. Billioux will miss the October meeting.
- The BSOs are always available prior to the meeting for any questions or concerns on reviews.

Adjournment

The meeting was adjourned by Dr. Malech at 4:27 PM.

Next meeting: October 01, 2025