

University of Washington
September 21, 2017 IACUC Meeting Minutes

Members Present:

| | | |
|----|------|--------------|
| AB | JM | ML |
| AS | JS | PB |
| CG | JFI | LJE (remote) |
| CH | KL | TB |
| JB | JPVH | |

Members Absent: SH SL JLS

Opening Business

The IACUC Chair called the meeting to order at 2:31 pm

Confirmation of a Quorum and Announcements

Quorum confirmed.

Protocol Review

- **TR201700057 (2225-06) – KSH**

This lab is evaluating the potential of human embryonic stem cell-derived/induced pluripotent stem cell-derived cardiomyocyte (hESC/iPSC-CM) as a new treatment to restore heart function in patients with heart diseases. They use non-human primate models to study the efficacy and side effects of their cell product and investigate a clinically relevant cell delivery method.

Reason for FCR: 18 unexpected events over the last 3 years of protocol activity. One animal had 2 unexpected events so total number of animals 17. 2 of these 17 animals completed the study, 11 were euthanized early and 4 animals died.

Total number of animals enrolled in experiments over the last 3 years: 35

Total number of animals who experienced unexpected events over the last 3 years: 17

Total unexpected events = 48%

The PI, by phone before leaving the meeting, addressed a question about suitability of the model.

Motion: A motion to approve the triennial as written was made and seconded.

Discussion: This is the first protocol doing work of this kind (stem cell repair of major cardiac damage) with a model of this kind (non-human primates). Given the highly innovative nature of the research, the unusually high rate of adverse events is not unexpected. Animals are watched very closely throughout the study and events that do occur are usually caught quickly and responded to quickly. Actions have been taken to improve the protocol after each adverse event, including the temporary removal of perches to prevent injury after surgery.

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Vote on the Motion: The amendment was approved with 13 members voting in favor, and 1 against.

- **AMEND201701268 (4314-07) – KSH**

This protocol proposes a novel HIV vaccination approach that uses persistent probiotic therapy as an adjuvant to enhance immunogenicity and protection induced by a potent combined SHIV vaccine (SIV DNA + HIV gp140 trimer). These studies will:

- 1) provide new insights into the possibility of harnessing the microbiota to enhance vaccine responses, and
- 2) provide assessment of both innate and adaptive immune responses that may block or abort the infection at the site of exposure.

The current amendment adds a new arm to assess the impact of malaria infection on HIV/SIV vaccine responses and efficacy.

Reason for FCR: The type, number and frequency of biological samples collected over the course of the study.

Before leaving the room, the PI answered several questions relating to the course of the study, similar studies, and result so far.

Motion: A motion to approve the amendment as written was made and seconded.

Discussion: This is an intensive study looking at the impact of gut microbiota on immune responses. For animals that are on study, sample collection may lead to potentially painful adhesions, which are evaluated prior to each biopsy (per UW Adhesion Grading Scale in NHP policy); the frequency and extent of adhesions that have been seen is no higher than expected, and no animals have failed to meet their endpoint for any reason. The need for and effect of separately housing animals during portions of the study was also discussed.

Vote on the Motion: The amendment was approved with 12 members voting in favor, 1 against, and 1 abstention.

- **AMEND201701511 (4316-01) – Amendment with Repair Surgery – JFI**

This is a primate neuroscience protocol. The goal of this group's work is to better understand the neural mechanisms that underlie memory processes, and characterize neural signals that support memory formation.

This amendment has two parts – it requests a repair surgery for one animal on study, and it also requests to add an animal and an MRI time point to Study C, project 3A.

Repair: The group is requesting 1 repair surgery for A13225, a 14 year old male rhesus macaque. This animal was moved here from Emory University in 2013. He currently has a head post and a recording chamber, which were both implanted at Emory prior to transfer. Since his transfer from Emory, the only surgery he has undergone is repair of his craniotomy

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this past July. The group reports that this monkey has been trained over more than 10 years on a large number of complex behavioral tasks and he has an optimally placed recording chamber, making him an invaluable animal for this study.

On his clinical history, the only thing I noted were some recurring chamber infections that responded to antibiotic therapy, and it looks like he's been otherwise very healthy.

Behaviorally, this animal has minor alopecia, no other behavioral concerns. He's currently singly housed due to a permanent veterinary exemption, specifically a history of incompatibility at his prior institution.

The other part of this amendment requests to add 1 animal and an MRI time point to Study C, project 3A. The goal of this project is to evaluate a new cranial implant, designed to house chronic or semi-chronic electrodes. This cranial implant is still in the design phase – animal work has not started. They initially requested 2 monkeys with which to validate their final design, but they found that they have two design options that they want to evaluate in vivo. Specifically, although both prototypes are made of PEEK, a type of plastic used in bone grafts and dental appliances, they want to determine whether a thin layer of titanium would cast a significant artifact on MRI, and also whether a “porous” treatment of the PEEK is preferable to the solid standard version in terms of bone growth into the implant. They are requesting to add one additional animal, so that they can use 2 animals to evaluate these variables, and the implant with the best fit and highest compatibility will be validated on the third animal. Animals on this project are already approved to receive a baseline MRI, but for this evaluation they also want to add an MRI time point after the cranial implant surgery.

Motion: A motion to approve the amendment as written was made and seconded.

Discussion: There was no discussion.

Vote on Motion: The amendment was approved with 13 members voting in favor and 1 against.

- **PROTO201600739 (2326-09) Animal Transfer – JFI**

This amendment requests to transfer one monkey, A14229, from protocol 2326-08 to protocol 2326-09. This group studies noninvasive vagus nerve stimulation (VNS) to augment targeted neuroplasticity and enhance cognitive performance.

This animal is implanted with a halo head stabilization implant, a vagus nerve implant, and a brain electrode implant. This animal will not receive any additional surgeries, other than repair surgeries, after protocol transfer. However, because potential repairs may qualify as major survival surgery, a USDA Exemption is required, as outlined in USDA Animal Care Policy #14. As part of that exemption request the group must specify the number of operative procedures to be performed and the time frame for the exemption, in addition to providing scientific justification. The group has requested an exemption period of 2 years, with a maximum of 2 repairs for each of the animal's implants. Repair surgeries will still need to be reviewed and approved by the IACUC individually. The projects on these two protocols are very similar – the 2326-09 protocol is the result of DARPA's requirement to have a stand-alone protocol. The reason for the transfer and exemption is 2-fold: The group argues that the animal is highly suitable for the behavior studies on protocol 2326-09, which require the same implanted hardware, and there are also budgetary concerns that require this animal to be supported by DARPA funding if he is to stay on study.

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Motion: A motion to approve the amendment as written was made and seconded.

Discussion: There was discussion about the animal's potential better suitability for the second study.

Vote on the Motion: The amendment was approved with 14 members voting in favor.

- **AMEND201701466 (4268-01) – AS**

I will be presenting a summary of an amendment for IACUC protocol 4286-01 *Adolescent Alcohol Exposure and Reward Processing*. This amendment is being reviewed by the full committee because it is requesting an exception from *The Guide* and from the UW IACUC's policy on *Rodent Cage Sanitation Frequency*. The IACUC needs to consider the welfare of the animals when granting this exception.

Background:

According to the *Guide*, "The frequency and intensity of cleaning and disinfection should depend on what is needed to provide a healthy environment for an animal. Methods and frequencies of sanitation will vary with many factors..." The optimal sanitation schedule is one that is frequent enough to maintain cleanliness and prevent disease, while providing minimal disruption to the rodent microenvironment. For standard SPF rodent housing of healthy rats in static cages, the UW IACUC's policy on *Rodent Cage Sanitation Frequency* requires that cages be changed at least once or twice a week, depending on the size and number of rodents in the cage.

Summary of this amendment:

Adolescent rats (21 days old) on this protocol are housed in standard static rat cages, split in half with a divider so that they are singly housed, two rats per cage, with a micro-isolator top on the cage. The group is proposing to house animals in the same static cage for nine days instead of the typical seven. This will occur the first nine days after arrival; after the first cage change the static cages will be changed every seven days. For example, if animals arrived on 8/9/17, their first cage change would be on 8/18/17, the next would be on 8/25, then 9/1, and so on. This exception would apply to all studies on this protocol.

The group is requesting this change to minimize stress experienced by new animals after transport, and to help these animals acclimate to their new environment. The lab has a standard practice of changing cages every Friday. Animal orders arrive on Wednesday. Rather than disturbing the animals 2 days after arrival with a cage change, they request additional time for the animals to acclimate by delaying the first cage change to the following Friday.

One concern related to the extended duration between cage changes is the buildup of ammonia, and the effect that this may have on the health and well-being of the rats. There is some discussion in the literature on this topic; two such papers were included in the IACUC meeting folder. In the interest of time, I am not going to go in to detail on the data presented in each paper, but will provide a summary instead. Both papers investigated how cage-cleaning frequency impacted ammonia levels, and the effects that the cage change frequencies had on the general health and well-being of rats. The papers evaluated various cage change frequencies between two times per week to once every 2 weeks. Both papers concluded that the longer duration cage change frequencies did not lead to an increase in ammonia levels that

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would have a negative impact on animal health (i.e., all levels measured were below 25 ppm).

Notably, these studies used different nesting materials, cage types, and caging densities compared to what the group is currently using. This is important to consider since each of these factors can impact the accumulation of ammonia and the impact on animal health. The group currently uses corn cob bedding, and rats are housed so that they each have approximately 68 in² of floor space. The studies in the papers used cellulose, sawdust or wood shavings as bedding. Corn cob bedding is generally believed to be of a similar absorbency to cellulose, and more absorbent than sawdust or wood shavings. The current floor space provided by the group, 68 in² per rat, is more than the majority of the scenarios tested within the papers, which evaluated housing densities that allowed from 17.5 in² of floor space per rat to >70 in² of floor space per rat.

Taken together, I think one could reasonably conclude that the request for an additional 2 days between cage changes should not have a negative impact on the health and wellbeing of the rats.

Motion: A motion to approve the amendment with modifications was made and seconded.

Discussion: There was discussion that the IACUC would like to request that the group use indicators that measure ammonia levels in the air within the rat cages and report back to the IACUC in order to gain valuable information on the difference in ammonia levels on day 7 compared to day 9 since last cage changing. An amendment to the motion was made and accepted to include use of the ammonia indicators.

Vote on the Motion: The amendment was approved with 14 members voting in favor.

- **PROTO201700184 (4365-02) – JFI**

Full Committee Review was requested for this new protocol due to the nature and invasiveness of the model

The objective of the proposed research is to investigate the feasibility, safety and tolerability of boiling histotripsy ablation (BH) of prostate cancer (PCa) using a small preclinical transrectal device. They will investigate this using a canine model of prostate cancer. They are requesting to use 26 hounds for this study. The dogs will initially be immunosuppressed with oral cyclosporine, and after serum levels are stabilized in the therapeutic window, canine prostate cancer cells will be injected into the prostate via ultrasound-guided percutaneous injection. The dogs will then be monitored for tumor growth by physical examination and weekly transrectal ultrasound. Once tumors reach ~ 1cm in diameter, which they anticipate to take 2-3 weeks, they will treat the tumors with boiling histotripsy via a transrectal focused ultrasound transducer. Some animals will be euthanized immediately after treatment, and others will be survived for up to 14 days. 4-6 dogs will be used for initial optimization of tumor implantation and establishment of tumor kinetics, 2 dogs will receive histotripsy without tumor implantation, and 18 will be used in the powered study.

The group's rationale for using a canine model is because canines are the only large quadruped animal that has an anatomically similar prostate to humans. Additionally, canines develop benign prostatic hyperplasia and prostate cancer that is similar in tissue morphology

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to humans. The argue that smaller models, in addition to having low homology with the human prostate, are also of inadequate size to permit evaluation of a clinically relevant pre-clinical prototype transrectal focused ultrasound device.

Motion: A motion to approve the protocol as written was made and seconded.

Discussion: There was additional discussion as to the reason for the protocol being reviewed in a convened meeting of the IACUC and it was reiterated that it was a new model to the university and is invasive in nature.

Vote on the Motion: The protocol was approved with 13 members voting in favor and 1 against.

Approval of the IACUC Meeting Minutes

The IACUC Chair called for the approval of the August 17, 2017 IACUC meeting minutes.

Motion: A motion to approve the minutes as written was made and seconded.

Discussion: None

Vote on the Motion: The meeting minutes were approved with 12 members voting in favor and 2 abstentions

Attending Veterinarian's Report - TB

Facility issues:

Humidity: No issues reported.

Temperature and lights:

9/7/17: In one primate room, one bank of lights remained on overnight instead of turning off as they should have. The problem has been fixed and the animals were not on study.

Protocol Monitoring:

There are 17 active protocols on the veterinary monitoring program (due to surgery, anesthesia, or other issues). I am adding one protocol (4389-01) to the veterinary monitoring program. A member of the IACUC asked that I add this protocol which utilizes surgery in zebrafish to study heart regeneration.

Adverse event:

Protocol 4265-01: One female rat was found dead in the cage on 7/1/17. The rat was implanted with a peripheral nerve interface near the bladder on 6/29/17. On gross necropsy, there was dehiscence of the abdominal wall, which was associated with sutures that did not consistently extend through the abdominal wall to catch the fascial layer and knot tying that was insufficient. The skin incision was intact. There was also a clot present in the abdomen. Based on histopathology, the cause of death was suspected to be associated with complications from the surgery. The group member who performed the surgery had taken the surgery classes, but had not been certified. He has since been re-trained, observed by veterinary staff, and certified. The incident has been reported to OLAW.

On 8/23/17, a rat died under anesthesia during a surgery. The cause of death has not been determined at this time (histopathology is still pending but there was evidence on gross exam of a pre-existing cardiac condition). The individual doing the surgery was not certified, and the person that was supposed to be observing him was not present during the entirety of the surgery. When this incident was brought to the principle investigator's attention all surgeries were temporarily suspended in the lab. The lab is working with AUTS to have more members certified in surgery and understands that uncertified members must be supervised for the entirety of procedures going forward. This will be reported to OLAW.

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Motion: A motion to send a letter of council to the group was made and seconded.

Discussion: The IACUC will send investigator a letter of council asking how he is going to ensure that surgeons are certified or appropriately supervised and asking him to come with a better solution to conveying the importance of this situation to new members of the lab. Liaison meeting can be used to address issues like this.

Vote on the Motion: The motion was approved with 14 members voting in favor.

HBA Subcommittee:

The HBA committee met this month and discussed incidents of morbidity and mortality in USDA species. In addition, questions were discussed regarding the full committee reviews on today's agenda.

OAW Director's Report – STI

The Director had no issues to report.

HoverBoard update was done on September 5, 2017 and a patch is going in on September 25th for minor issues.

At the October IACUC Meeting the Committee will start talking about the next semi-annual report. We will be bringing portions of the next semi-annual starting next IACUC meeting. OAW will also be bringing a proposal to cut back on the number of visits for labs that have a perfect record on Site Visits resulting in 1 site visit per year rather than 2 site visits per year.

One IACUC Member left the meeting

Other Business - STI

A letter was received from the Primate Center responding to the letter from the August meeting regarding non-human primates that were left overnight in a trapping cage. The IACUC was reminded that there were no adverse events associated with this incident, and a letter was sent to identify actions that the Primate Center will take to prevent future occurrences. The response apologized for the incident and stated that the Primate Center had taken the following actions as a result: reassigned and retrained the staff member involved; and reviewed the use of the buddy system and implemented this as a plan of action going forward. Originally only implemented in I-Wing and is now fully implemented in all facilities in Seattle. The Center also found no evidence of miscommunication playing a role in this incident.

Closing Business:

The Meeting was brought to a close at 4:14 pm. The floor was opened to public comment.