

University of Washington
July 21, 2016 IACUC Meeting Minutes

Members Present:	AS	JB	MG
	CG (Scientist)	JM	ML
	CG (Public)	JS	SH
	CH	KH	SL
	EC	KL	TB

Members Absent:	AB	MB	MT
	CJ	ML	NK
			PB

Opening Business:

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

Protocol Review

Dr. Fetz 2326-08, V.123 "Brain-computer Interface for Primates"

KSH presented the Significant Change to the Committee.

Per the UW IACUC policy entitled "Guidelines for Non-Human Primate Neuroscience Studies", decisions regarding requests for additional repair surgeries must be made at convened meetings of the IACUC. The policy states that relevant protocols can and should include provision for one or two repair surgeries, and these requests must include justification of the need for that specific animal to continue on the study, as well as a complete medical history.

Background:

This project investigates the mechanisms of cortical plasticity in nonhuman primates and is developing methods and techniques for inducing and controlling adaptive plasticity. The knowledge and technology generated by this project are vital for the development of neuro-rehabilitation treatments after stroke and brain injury.

The group is requesting one repair surgery for A14231. This animal is a 5-year old male Rhesus macaque who has been enrolled in this study since July 2014. This animal's continued participation in the project is critical to its success due to his extensive training in a bimanual task and his production of useful data to study the effects of Vagus-Nerve Stimulation (VNS) on cortical plasticity. This animal has received five experimental and one clinical surgeries.

Experimental surgical history:

- 04-08-15 - Experimental surgery to implant VNS electrode and generator implant
- 04-20-15 - Experimental skull surgery for a cranial implant
- 01-14-16 - Vagus nerve cuff implant - Subcutaneous wire between generator and chamber
- 03-10-16 - Repair surgery to remove VNS (generator) - Generator/wires were explanted. New wires were routed through a different tunnel.
- 06-09-16 - Repair surgery to remove old VNS lead extension. New VNS lead extension was implanted on the left upper chest/neck region

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Clinical history:

- 05-04-16 - Surgery to debride and repair ulceration over collector on chest.
- 06-27-16 – Vet staff began treatment for implant erosion (non-surgical, anesthetic event)

Behavioral history:

- This animal was referred to Behavioral Management Services (BMS) in December 2014 for self-injurious over-grooming, but no further wounding was observed after December.
- Some moderate to severe alopecia (or hair loss) was observed, so this animal was enrolled in the Leafy Greens study to see if providing this extra form of enrichment would help with the alopecia. The alopecia did eventually improve, though it may not have been due to the provisioning of the leafy greens (overall effect across subjects was not significant in this study.)
- Alopecia remained at a lower level until January 2016 but has improved since. The animal still has some low level alopecia.
- Observations by BMS indicate that this animal is not engaging in any serious abnormal behaviors, though he has engaged in some minor, infrequent stereotypies.
- This animal remains flagged as “Behaviorally Sensitive” due to original referral for self-injurious over-grooming. This means that in addition to standard environmental enrichment (EE) that all animals receive 7 days a week, he receives additional EE 3 times per week.
- This animal is currently individually housed in a convertible cage, meaning he has vertical access to two cages. He has a temporary exemption from social contact in place due to the lack of an appropriate social partner, SRV+ status and experimental implants. This exemption is reviewed by a WaNPRC veterinarian (who is acting as a designee for the AV) on a monthly basis in accordance with the Animal Welfare Act.

Current status:

- The animal is reported to be healthy.

Plan for the new repair surgery:

- The group is not completely certain about the root cause of the recurring hardware erosions, however the absence of any granulomatous tissue reaction or purulent drainage leads them to believe that a foreign body reaction (“rejection”) and/or implant infection are not the culprits.
- Impaired tissue vascularity may play a role, due to the numerous procedures the animal has had to date in the chest region. Another contributing factor may be pressure necrosis that the hardware exerts against the already thin and now atrophic skin. Because these latter two factors are localized to the chest, and not systemic issues, the group believes that if they surgically re-route the electrodes to a different skin area, they may achieve a lasting solution conducive for them to safely continue the VNS experiments.

The significant change provides a description of the planned surgical approach and an alternative if this approach is unsuccessful. Note: This alternative approach will be requested in an additional repair surgery request.

Scientific justification for a new repair surgery:

This animal is uniquely valuable to the research for the following reasons:

- He is the only non-human primate in the lab and, and possibly in the world, that bears a VNS cuff electrode. This animal has a cortical implant that performs exceptionally well, with no signal quality or clinical issues. This animal is the most consistent performer on the behavioral task for which he is trained among all the animals in the group. This makes him the best candidate for measuring subtle

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behavioral effects of VNS.

- During the past year, the group has collected much data from this animal on effects of VNS on cortical function. This was the first part of the VNS project, a required step before advancing to the second, main part of the project, which focuses on the effects of VNS on cortical plasticity. The group had to stop experiments with this animal and could not advance to the second part of the experiment. If the repair surgery for this animal is not approved the group would have to spend another year collecting similar data from another animal, only to start collecting data on VNS and cortical plasticity for the first time. The same sequence of experiments would then have to be repeated with yet another animal, delaying the entire project by at least 1 year in total and, of course, requiring the addition of another nonhuman primate to this protocol.
- The surgical challenges the group has encountered with this implant have been significant, despite the surgical expertise of the personnel involved. This, however, is not uncommon with novel, complicated techniques. Through the difficult process of repair surgeries, the group now has a much better understanding of the biological response to this implant and the surgical limitations associated with it. The group will make use of this knowledge and experience with future surgeries, in this and other animals, to minimize complications.

CG asked the researcher if the repeated surgeries had any impact on the test data. The researcher replied that there is no measurable impact. The signals are fine and the animal is performing tasks consistently.

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

Discussion: CG commented that there are plans to utilize the requested repair and questioned the need to include another repair so that they would have one available. The Committee discussed the animal's clinical history and the past rejection of the VNC implant. CH explained the proposed approach to the Committee, which she thought had a good chance of working. The Committee discussed the proposed plan and potential next steps if it was not successful. It was noted that the protocol was on veterinary monitoring. STI, commented that moving forward, there is the opportunity to observe specific animals during site visits and as part of the IACUC records review.

Vote on the Motion: The Significant Change was approved with 13 members voting in favor and 2 members opposed.

Approval of the IACUC Meeting Minutes

The IACUC Chair called for the approval of the June 16, 2016 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 13 members voting in favor and 2 abstentions.

The Benefits of Research - JS

Our Benefit story this month is on AIDS research at UW. Our focus on AIDS was suggested by IACUC member MG, who was inspired by the story behind this recently issued Wheaties box featuring Greg Louganis, an Olympic gold medalist in the 1980s who was excluded from the Wheaties box back then because he was rumored

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to be gay, and didn't fit the 'wholesome image' the General Mills company was looking for. Louganis later came out publicly and revealed his HIV-positive status in the mid-90's. As Louganis noted in a recent NPR interview, 'Back in '95, I wasn't expected to live very long because we thought of HIV-AIDS as a death sentence, so to be here today, now 56 [years old], the box means so much more to me than it would have then because I feel like I'm being embraced as a whole person, not just for my athletic achievements.' [<http://www.npr.org/sections/thetwo-way/2016/04/05/473107455/better-late-than-never-olympic-champion-greg-louganis-gets-his-wheaties-box>] This serves as a poignant reminder that because of animal research, AIDS patients are now living longer, healthier lives. AIDS research, often using non-human primates, involves some of the toughest decisions the IACUC needs to make about risks to the animals and the researchers who perform the studies. Both human and non-human primates are heroes in this story, which reminds us of the very real benefits that have come and will continue to come from the UW labs doing this important work on HIV-AIDS.

Attending Veterinarian's Report

Facility issues:

- **Humidity:** No recent reports of low humidity
- **Temperature and lights:** None

Protocol Monitoring: There are 15 active protocols on the veterinary monitoring program. Nine involve surgery, anesthesia and surgery, or restraint and surgery. Five involve other procedures including one that involves tumor monitoring.

Adverse events:

- Protocol 4374-01: The purpose of this research is to study the mechanisms involved in tissue regeneration utilizing *Xenopus tropicalis*. On 6/16/16, the group was transferring frogs from one tank to another when one frog got out, jumped away, and eventually landed in a container of 3% bleach that was in the sink. The group removed it, rinsed it off, and put it in a high salt bath. Bleach is very toxic to frogs and the frog died within 30 minutes. The group has since removed bleach from the room where live frogs are present and all use of bleach will occur in a separate space. This event has been reported to OLAW. No action was taken by the IACUC.
- GNAC: Four 3-month-old female germ free C57BL/6 mice were moved from a sterile isolator to a positive pressure ventilated caging system on 5/19/16 using standard sterile procedures per GNAC (gnotobiotic animal core) SOP. The next day, all four mice were found dead in the cage. Food and water were present in the cage and water appeared to easily flow from the water bottle. The cage was examined at the time of identification and confirmed to be docked appropriately on the rack; however, there were varying degrees of debris and dust noted within the exhaust air valves of the rack. All other mice housed on this rack appear healthy and stable. The dead mice were submitted for necropsy and histology. No clear cause of death was determined, but the personnel in the GNAC are concerned that build-up of dust in the air outflow track limited air movement in the cage and resulted in a build-up of CO₂. The SOP for these racks has been changed to have the exhaust air valves cleaned quarterly. This event has been reported to OLAW. No action was taken by the IACUC.
- Two approximately 3-week-old fledgling zebra finches were found dead in the cage. One on 5/19/16 and the second on 5/23/16. In both cases, the position of the carcasses within the cage when found

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suggested that the fledgling may have been caught between the catch pan and the lower cage. Both animals were submitted for necropsy and histopathology. Mild subcutaneous hemorrhage and bruising were noted over the dorsal neck in the first case and no significant lesions were apparent in the second. Histopathology showed no evidence of significant soft tissue or bony trauma or any other lesions in either bird that would contribute to the death of the animal.

Cages were thoroughly examined and determined to be in proper working order. However, when the cage pans are removed for cleaning, it is possible for birds to fly beneath the pans when they are being placed back into the cage, and it is believed that this is what happened in these incidents given that neither animal had evidence of trauma. Lack of available water in that space under the pan may have contributed to the death of these animals. All staff have been updated regarding the incidents and husbandry procedures have been reviewed. DCM is working to modify the caging system to limit the space in which birds can fly into underneath the pans. A picture of the cage was circulated for review. The Committee discussed past issues related to finch housing. This event has been reported to OLAW. No action was taken by the IACUC.

HBA Subcommittee:

The HBA committee this month met and discussed the potential clinical consequences of intestinal resections in non-human primates and is working on a proposed IACUC policy regarding this procedure which we hope to present at the next IACUC meeting. We also discussed clinical cases. Any interested IACUC member is always welcome to join this subcommittee.

OAW Director's Report – summary slide in meeting folder

Protocol Review Continued

Dr. Phillips 4146-01, V.67 “Electrical Stimulation of the Vestibular Nerve”

KSH presented the Significant Change to the Committee.

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Background:

The goal of this protocol is to develop a viable implantable prosthesis to help patients with dizziness, balance and orientation problems to regain their mobility and active lives. To do this, the first step is to understand whether it is possible to implant a stimulating prosthesis in the vestibular end organ of the inner ear and obtain activation of the balance structures in the brain that is similar to normal activation. The second step is to discover if the prosthesis can elicit behavior that is similar to normal behavior. Finally, it must be determined if the prosthesis can be used to substitute for natural stimulation when the vestibular end organ no longer functions normally. All of these steps, performed in Rhesus macaques using

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modifications of existing human implant technology, can provide for a rapid progression toward implementation of a human prosthesis.

These current studies examine ways to optimize electrical stimulation to treat a variety of human vestibular conditions, including below normal or absence of bilateral vestibular function, unilateral vestibular loss, Meniere's disease and central vestibulopathy, with and without hearing loss.

The group currently has FDA approval for their first human safety and efficacy study for a single application of the device to treat advanced unilateral Meniere's disease based on the results of this project to date.

The group is requesting two repair surgeries for Z11090. One will be used immediately for an eye coil and lug repair surgery and the second will be "banked" for future use. This animal is a 5-year old male Rhesus macaque who has been enrolled in this study since February 2016. This animal's continued participation in the project is critical to its success due to his significant training. This animal has received two experimental and one clinical surgeries.

Experimental surgical history:

05-16-16 – Implant eye coil and lugs

05-23-16 – Repair lug surgery

Clinical history:

06-21-16 – Rostral lug implant removed

Behavioral history:

This animal was reported to WaNPRC Behavior Management Services (BMS) for displaying floating limb. Floating limb (as described in WaNPRC SOP Addendum 0740A – Behavior Monitoring Definitions) is when, in an apparently non-volitional manner, a monkey's limb (usually the leg) is elevated. The monkey may be startled by the limb, may communicate with the limb as if it were not his own or may bite the limb. This does not include elevating the limb volitionally to groom it or rest it on parts of the cage, etc. Neither floating limb, nor any other abnormal behaviors have been observed by BMS staff and behavior observations have been performed numerous times, beginning in November 2015.

This animal currently receives standard environmental enrichment (EE) 7 days a week and is currently in a stable social contact environment via grooming-contact bars.

Current status:

The animal is reported to be in excellent health.

Scientific justification for repair surgeries:

This animal is a critical part of the study to evaluate the feasibility and design of a viable prosthesis for human implantation and this animal will provide essential data for the group to continue their work. This animal has been significantly trained over several months and is therefore very valuable to the project. The group has invested a large amount of time and effort to train this animal for testing, and replacing this animal with a new, naïve animal would be a loss of valuable time and effort, on both our behalf and the animal's, and it would require an additional animal to be used on the protocol.

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

Discussion: None

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Vote on the Motion: The Significant Change was approved unanimously with 15 members voting in favor.

IACUC SOPs and Policies

Housing and Care of Vertebrate Animals

The IACUC reviewed the policy on Housing and Care of Vertebrate Animals and the IACUC voted to approve the policy after removal of the section on how to process requests for exceptions, retaining the sections on housing and procedure locations and animal husbandry.

Motion: A motion was made and seconded to approve the revised policy.

Vote on the Motion: The revised policy was approved with 14 members voting in favor and 1 abstention.

STI suggested that globally, the IACUC should consider how to handle exemptions to all IACUC policies. The Committee discussed the practicality of this proposal.

Semiannual Program and Facility Review

The OAW Manager of Regulatory Programs briefly summarized the report that had been previously sent to the Committee. The IACUC was reminded that the Concurrence sheet was due by July 30, 2016.

HoverBoard – EC reminded the IACUC that the migration of protocols into HoverBoard is in progress and IACUC members would be doing many of these reviews in the system. EC reminded members of the location of help documents and that they should reach out to OAW with any questions.

Closing Business:

The Meeting was brought to a close at 4:13 pm. The floor was opened to public comment.