

TRiM Translational Advisory Committee (TAC) Meeting Notes February 20, 2024

Members Present: Kriya Dunlap, Chair, Kelly Drew, PhD; Nicholaas Deutz, PhD, MD; Judith Kelleher-Andersson, PhD; Daniel Promislow, DPhil; Greg Pietsch, DVM; and Denise Daniello, MA (ex officio)

Meeting Purpose: Update the TAC regarding the new canine cognitive dysfunction (CCD) assessment project and discuss how the canine model fits with TRiM's translational focus.

Discussion

1. *CCD Project Update* – Greg Pietsch summarized this project that received \$10,000 grant funding from NeuroNascent Inc. The purpose of this study is to assess the prevalence of CCD among dogs in Interior Alaska. TRiM is sponsoring an event this evening at Pike's Landing to raise awareness about the CCD project among local veterinarians and to introduce diagnostic techniques, such as the CADES questionnaire that tests behavioral symptoms of CCD. We have 10 local veterinarians and their staff signed up to attend. TRiM's goal is to build a network of local veterinarians who use the CADES questionnaire as part of their assessment and can supply eligible canine patients for this study. We want to recruit veterinarians who are interested in tracking older medium-sized dogs, between 8 to 11 years, that show symptoms of CCD (anxiety, functional loss, anosmia, soiling, repetitive behavior, etc.), which are similar to Alzheimer's disease. CCD is a neurodegenerative disorder that is estimated to affect 30% of older dogs. Our goal is to scan two dogs using the MRI that test mild to moderate based on the results from the CADES questionnaire to establish a baseline. The MRI will track changes in hippocampus volume over the 3-year study period and bloodwork results that identify CCD blood biomarkers. Owners will not have to pay for the physical examinations or testing as part of the study as they will be covered by the grant funds. Owners will be trained in using the anosmia test to assess changes in their dog's smelling ability during the project time.

Greg also cited three recent news releases about the CCD project. They include a press release that appeared in the UAF News and Information, the KUAC radio interview, and a third interview is scheduled for the KTVF news. These news items are posted on [TRiM's website](#).

Dr. Promislow updated the TAC about the Dog Aging Project and his recent career move. He has accepted a new position as Senior Scientist with the Jean Mayer USDA Human Nutrition Research Center at Tufts University. The Dog Aging Project at UW is in its final year of NIH funding. Their last NIH U19 submission was not funded, and the plan is to resubmit in May 2024. There will be a 10-month period when the Dog Aging project will have no NIH funds. To keep the initiative alive, Dr. Promislow and other researchers created the non-profit Dog Aging Institute, which if successful, will generate funding to support the Dog Aging project and related canine studies through smaller grants, private donors, and corporate sponsorships to keep the project going until the NIH U19 grant is funded.

Dr. Promislow noted a few researchers who may be good contacts for the Alaska CCD project. Stephanie McGrath and her post doc have both been involved with canine research at the University of Colorado and have experience using MRI imaging. In addition, there is a veterinary ophthalmologist at the University of Wisconsin who is interested in neurodegeneration in the eye and may be a good resource.

2. *Using the Canine Model and its Fit with TRiM's Translational Focus* - Kelly described the purpose of COBRE grants is to build infrastructure for biomedical research and summarized TRiM's developments since the start of the COBRE. Alaska and Wyoming are tied for last place when it comes to NIH funding than any other state in the U.S. TRiM started with hibernation as our discovery platform and found that

there are many adaptations related to metabolism and regeneration. Hibernators in Alaska suppress their metabolism to conserve energy but also maintain their muscle mass and brain throughout hibernation potentially using anabolic pathways, which is a focus for TRiM's research. TRiM's investigators are examining how hibernators use anabolic pathways to maintain muscle mass. Sarah Rice worked with PI Khrys Duddlestone on her COBRE funded project and found that arctic ground squirrels recycle nitrogen using gut microbes. Anya Goropashnaya's research is looking at muscle regeneration during hibernation. Judy Kelliher-Andersson has a drug in development to treat Alzheimer's disease, but this involves a long process getting FDA approval for clinical trials.

While TRiM's research is basic observational science, Kelly explained, our discoveries have the potential to develop into potential therapies. COBRE provides an infrastructure to funnel these discoveries. Trey Coker observed that Fairbanks does not have physicians to provide clinical oversight for human intervention studies, which was a significant barrier for him to continue his clinical trials here. However, we do have clinical oversight for dogs with vets and vet students involved in the UAF veterinary medicine program. TRiM can tap into the pipeline of MRI users and the vet med program with discoveries made from hibernation that we hope will inspire new targets that can be applied in clinical scenarios. Kriya Dunlap has found that diet and lifestyle makes a difference in a dog's health. Interventions that work in dogs as human sentinels, namely through nutrition and exercise, could also work for people. By following their vet's advice regarding what to feed their dogs and the importance of exercise, dog owners might adopt these behavioral interventions and benefit themselves. Building a translational pipeline is the connection between hibernation discoveries and the canine intervention platform to provide research opportunities that make a difference in human health.

One TAC member suggested reaching out to Fauna Bio to form a partnership as they are a company built on the biology of hibernation. They are interested in obesity and how hibernation adaptations can be applied to treat this disease and Alzheimer's. Fauna Bio has recently formed a partnership with Eli Lilly, a major pharma company, that could develop a philanthropic arm for research. Reaching out to Fauna Bio was initially dismissed because this company is focused more on informatics and not on translational research. The idea was later reconsidered as they could be a significant funder for hibernation research and potential applications using other comparative animal models to study a variety of diseases. Another member encouraged TRiM to maintain hibernation as a focus for TRiM's research because hibernation is a unique research area for Alaska. However, it is difficult to understand the connection between dogs, hibernation, and translational research.

Kelly suggested that TRiM's research projects be placed on the next agenda to update the TAC on the projects that we are doing to show that we are not just focused on canine research. We have projects that are attempting to identify mechanisms using cell cultures that contribute to neuro-regeneration during rewarming in the AGS. Another project is examining the role of the gut microbiota to support muscle regeneration in the AGS model. We also have a bear project that is mostly related to how metabolic suppression works during hibernation and whether this mechanism is sleep related. Kelly's research focuses on developing a drug formulation that can mimic a hibernation state for cooling and could be used in remote emergency and neurocritical care situations. We are still trying to learn how to develop translational capacity from what Trey Coker learned doing his clinical trials. Trey Coker hit roadblocks due to not having onsite clinical oversight and problems recruiting human subjects.

It was also noted that TRiM has two parallel research paths for hibernation, serving as the discovery platform, and the canine model as an interventional platform that feed into TRiM's translational pipeline. We are using different comparative models to develop TRiM's translational pipeline to treat

age-related disease. The point of intersection might be metabolism that could play a significant role in the aging process. Through partnerships with UAA and others, Kelly noted, we can expand the Center's pipeline for translational research.

3. What types of translational research projects can TRiM pursue given our resources, investigators, interests, and infrastructure capacity? What sets TRiM apart from other research centers that focus on metabolism and aging?

Kriya noted that we should focus on resources that are unique to us in Alaska. Our locally grown food sources, such as wild Alaskan blueberries, seaweed, and wild salmon with high vitamin D content have excellent nutritional value. Kriya also explained her use of canines as a "sentinel animal" as they have traditionally been used for subsistence and cultural activities, live in the same house as their owners, often eat the same foods (such as salmon) as their owners, and live in a cold climate. Judy added that dogs are the "perfect translational model" because they are a fairly homogenous population and provide an excellent natural model to study age-related disorders in an accelerated time period as dogs age faster than humans. This is a unique area of study that shows promise for COBRE research that focuses on adaptations to extreme environments and the impact on aging in extreme climate conditions. The group also discussed if cold arctic conditions and traditional foods might impact muscle performance (of interest to military stationed in Alaska), working and exercising under cold conditions, and aging. For example, it was observed that sled dogs that run regularly rarely develop cardiovascular problems. However, new research has shown that extreme endurance human athletes are developing cardiovascular issues.

The key for developing new research models for the renewal is to identify TRiM's strengths and limitations (such as technology) and find other people who have an interest in hibernation and strengths that complement TRiM's limitations. TRiM should focus on something unique to Alaska, that is different in a positive or negative way, and then follow-up and connect the research to something that we are already doing. For example, Dr. Deutz explained, TRiM can conduct observational studies by doing "one day" physiological studies (taking blood work or the effects of a typical diet) on different populations in different situations that would position us for an overall translational study involving human research. Sleep patterns affected by the seasonal extremes in daylight, high alcohol consumption, head injuries, and high rates of depression could be factors contributing to the growing numbers of Alzheimer's disease in Alaska, but these factors have not been well studied.

Everyone agreed that a meeting should be scheduled as soon as possible to develop an action plan for the ideas discussed that could be included in the COBRE renewal.

The meeting was adjourned at 12:30 (AK time).