UW College of Agriculture and Natural Resources

Global Perspectives Grant Program

Project Report Instructions

A brief written report must be submitted electronically to the AES office **within one month of returning from your trip**. Photographs supplementing the report are encouraged and are appreciated by the donor. Failure to submit a report may jeopardize future funding from AES.

In addition to forwarding these reports to our benefactor, reports will also be published on the AES website—do not include any photos that require permission to post to our webpage. Reports must be written in a style **understandable by the lay person** and may be edited for readability before being published to the AES website or the University of Wyoming Foundation report.

Format: Use 12 point type, single line spacing, and one inch margins. Submit your report to aes@uwyo.edu as a single PDF file.

Include the following information:

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1. COVER PAGE

Award Period (e.g. Spring 2012): **Spring 2022**

Principle Investigator(s) **Jason Gigley** **Department:** **MOLB**
Email: **jgigley@uwyo.edu**

Project Title from Application: **Understanding nutritional immunity and disease tolerance during Toxoplasma gondii infection**

Amount spent: **~$8000.00**

Non-technical summary (max 1500 characters plus spaces): Provide a one paragraph non-technical summary that most people can understand.

My global perspectives grant allowed me to travel to Portugal to the Gulbenkian Science Institute where I learned about 2 new areas of research, nutritional immunity and disease tolerance. There are two processes involved in the resistance of a host to an infectious disease. The first process is the development of immune responses to get rid of the infectious agent. The second process is the ability of the body to resist or tolerate this immune response so that our tissues containing the infectious agent don't just die causing the host to die due to organ failure during the infection. The first goal of this project was to understand how available iron works in the development of immune responses that are important for controlling the common food borne parasite *Toxoplasma gondii* in a process called nutritional immunity. The second goal of this project was to study how available iron works in the development of disease tolerance or the ability of the host tissues to resist the immune response during infection with this parasite. In Portugal, I was able to learn from my host lab and perform experiments to achieve these goals. We discovered that if we change the availability of iron in specific tissues

we impact development of immunity and the ability of the body to survive the infection. I am very thankful for this grant because it helped me develop international collaborations that will lead to future publications and grant submissions.

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2. REPORT: Maximum of two pages of text; in addition, please also include **photos**. Must be written in a style understandable by a general audience.

Include:

1. Main results of activities planned in the proposal**.**
2. Describe any future plans
3. Outline potential impacts to a) the College of Agriculture and Natural Resources, b) the University of Wyoming, and c) the State of Wyoming
4. Photos

QUESTIONS? Contact Joanne Newcomb in the Agricultural Experiment Station office at aes@uwyo.edu or (307) 766-3667.

Report:

1. Main results of activities planned in the proposal. Our objectives in this proposal were to modify iron levels in mice during infection with the obligate intracellular parasite *Toxoplasma gondii* (*T. gondii*) to see how changing the availability of this nutrient to the parasite and the host affected the development of immunity and the ability of the body to withstand the immune response important for clearing this pathogen called disease tolerance. We had originally planned to use a chemical based method to change iron levels with a drug called deferiprone. However, we realized that this method would target to many tissues in the mouse host. I was presented with the opportunity to take a different and better approach to address our questions. The laboratory of Dr. Miguel Soares generated mice that allowed us to manipulate iron levels in specific cells during the infection. We were still able to address the same objectives, 1) Investigate how nutritional immunity impacts *T. gondii* infection and 2) Dissect how disease tolerance impacts immunity to *T. gondii* infection. We used two different types of mice to address these questions. We used mice that had a cellular iron exporter genetically knocked out called ferroportin in cells called macrophages. We also used mice that had a cellular iron importer genetically knocked out called transferrin receptor in the same cells. Macrophages are important immune cells that provide early detection of the parasite and help activate the immune system as part of what is called the innate immune response. Macrophages are cells that the parasite likes to live in. They are also very important cells in regulating iron levels in the body. *T. gondii* is highly sensitive to iron levels, too much iron the parasite stops growing and replicating and too little iron also stops the parasite from growing and replicating. We measured for question 1 the health score of the animals which indicates how high the parasite burdens and the ability of the immune response to clear the infection. We also measured survival of the animals which also helps us determine how well the parasite infection is being controlled in the different animals. We expected that mice with macrophages that could not export iron would be toxic to the parasite and prevent its spread and enhanced survival. We expected that mice with macrophages that could not import iron would also be toxic to the parasite because the parasite now could not acquire iron. We expected to have decreased disease scores and increased survival of the genetically modified mice. The main results were that in mice whose macrophages could not export iron, the disease score was worse than in the control mice whose macrophages could still export iron. In the mice whose macrophages could not take up iron the disease score was much lower than mice that still could take up iron. The survival of animals that could not export iron was also lower than controls while the animals that could not take up iron, their survival was better. Therefore, our main finding for question 1 was for nutritional immunity, iron export in macrophages is required for better control of the parasite, while iron import in macrophages enhances parasite burdens and decreases mouse survival.

Our next question which was objective 2 was to assess disease tolerance during *T. gondii* infection and ask how iron export and import in macrophages affect this process. Disease tolerance requires what is called metabolic adaptation to help keep our tissues alive and prevent multiple organ failure. To assess disease tolerance in an animal we measure daily body temperature, blood glucose, weight and survival. We could not hypothesize what the outcomes would be from these experiments because disease tolerance has never been assessed during *T. gondii* infection. We first built a foundation of data measuring these

outcomes with just control mice infected with *T. gondii*. Infection usually in mice usually results in a quick drop in body temperature, blood glucose and weight that then recovers rapidly when there is disease tolerance to the infection. Unlike these other infection mice infected with *T. gondii* rapidly increased their body temperature and blood glucose for the first 5-6 days. Then they slowly decreased their body temperature, blood glucose, weight progressively over a longer period of time. We then assayed disease tolerance in the mice whose macrophages lack iron export and import. We did not observe a difference between knockout mice and control mice for body temperature, blood glucose or weight, suggesting that although iron export and import in macrophages is important for nutritional immunity, it does not appear to play a role in disease tolerance.

2. Future plans: Our future plans are to further explore how macrophage iron export and import contribute to nutritional immunity. We will be obtaining the mice that Dr. Soares generated and we will perform more experiments here in my lab at the University of Wyoming. We will also explore additional tissues and metabolic processes regulated by iron levels that could be involved in disease tolerance to *T. gondii* infection. The Soares lab is also performing additional experiments and we are currently planning to submit grants to fund these projects.

3. Potential impacts to a) the College of Agriculture and Natural Resources, b) the University of Wyoming, and c) the State of Wyoming. We have made a sustained positive impact on the College of Agriculture and Natural Resources, University and the state by learning about nutritional immunity and disease tolerance. We can now help teach our knowledge to students and other researchers. We have developed an international collaboration that will bring Portugese researchers here and Wyoming students to Portugal. This collaboration will also help generate revenue for the research enterprise at all levels.

4. Photos: Soares lab photo left, Dr. Jess Thompson and I in animal facility right.