

**BIOLOGY
BLUE ASH****SUMMER RESEARCH OPPORTUNITIES FOR UNDERGRADUATE WOMEN****APPLICATION DEADLINE: 03/01/2020****PROJECT TITLE: Elucidation of drug-receptor structure for the development of new drugs against brain-eating amoeba, Naegleria fowleri**

Yoshi Odaka
UCBA
9555 Plainfield Rd.
Blue Ash, OH 45236
yoshi.odaka@uc.edu

Project Description

The long-term goal of the project is to establish new strategies to develop rapamycin derivative drugs to fight against infectious diseases caused by eukaryotic cells such as amoeba, algae, and fungi. The specific aim of this proposal is to design and construct new rapamycin-derivative drugs that specifically target and inhibit the brain-eating amoeba, *Naegleria fowleri* (*N. fowleri*) that is resistant to rapamycin.

Naegleriasis has been reported in every continent, except Antarctica. The causative agent *N. fowleri* is a unicellular amoeba found in freshwater or wet soil. When contaminated water enters the nasal cavity, the amoeba gains access to the brain organ through the olfactory nerves. Although it is a rare infectious disease (145 cases in the U.S. between 1962 and 2018), its death rate exceeds 97% in the U.S. To make matters worse, the victims are typically young children (median age is 12). Because of its rarity, the funding to study *Naegleria fowleri* is limited. Typically, the infection occurs in the southern states, but more recently Naegleriasis was reported in northern states such as Minnesota, Indiana, and Maryland. The extremely high fatality comes from the fact that effective treatment has not been established. Moreover, the most commonly used drug, amphotericin B, is highly toxic not only to the amoeba but also to humans, severely damaging the liver and kidneys (potentially fatal). Therefore, the aim of this project is to develop new effective and non-toxic antibiotics against *N. fowleri*. The key data we need for developing effective drugs is the structural information of the drug-receptor, called FKBP, in *Naegleria*.

Recently, we discovered that *Naegleria gruberi* (a non-pathogenic species) is resistant to the drug rapamycin, which was originally identified as an antifungal agent and typically inhibits the growth of most eukaryotic cells (except plant cells). Further analysis of the drug-receptor in *N. fowleri* and

N. gruberi identified a region of the receptor that is unique to the Naegleria species and proximal to rapamycin binding site. Therefore, we hypothesize that this unique region in the receptor makes Naegleria resistant to the drug rapamycin by inhibiting the interaction between the drug and receptor. In other words, the structural differences between the Naegleria and human receptors can be exploited to design and synthesize new rapamycin derivatives that specifically target the Naegleria receptor but not the human receptor. Such drugs should provide specificity and efficacy against the amoeba while minimizing the toxicity to humans.