**Why is the drug praziquantel effective in the treatment of parasitic flatworms?**

Praziquantel (PZQ) is the drug most commonly used in humans and livestock to fight the disease schistosomiasis, an infection of the host by parasitic worms of the genus *Schistosoma*. While it has been used effectively for several decades, the mechanism by which it works is still unknown. Flatworms of the genus *Schistosoma* treated with PZQ experience tetanic musculature contraction resulting in paralysis due to a cellular influx of Ca\(^{2+}\) ions, which then allows the host organism’s immune system to eliminate the damaged worms (Bricker C.S., et al, 1983; Ismail M. et al, 1999). There is evidence that the mechanism of the drug has to do with its interaction with an unusual β-variant subunit of the voltage-gated Ca\(^{2+}\) channel present in susceptible organisms, which results from two amino acid substitutions in the primary structure of the protein. This is supported by the observation that an intracellular Ca\(^{2+}\) influx in response to PZQ can, in some cases, be conferred to previously nonsusceptible organisms which are made to express the variant β-subunit though recombinant treatment and cloning (Jezierski M.C., Greenberg R.M., 2006; Kohn A. et al, 2001). However, no proof of any direct interaction between PZQ and a specific site on the Ca\(^{2+}\) ion channel has been established. This has lead some to suggest alternative mechanisms whereby adenosine intake is inhibited, perhaps as an intermediate step in the pathway leading to Ca\(^{2+}\) influx (Angelucci F. et al, 2007). My project will evaluate the hypothesis that worms with reduced expression of the variant β-subunit due to RNAi treatment will require a more concentrated lethal dose of PZQ than an untreated control group, thereby providing more conclusive evidence implicating the variant β-subunit as the site of action for PZQ in the genus *Schistosoma.*
Identifying the specific site where PZQ acts would assist in the development of a more effective treatment for human populations against the disease schistosomiasis, which infects over 200 million people worldwide. There is also the potential for advancements in the development of drugs addressing the agricultural sources of diseases such as cysticercosis, the infection of the brain and CNS by flat worm parasites often spread through pork, which afflicts as much as 44 percent of the population in parts of West and Central Africa. (Zoli A, et al, 2003). Perhaps most importantly, a more complete understanding of how the drug works would allow scientists to combat the rise of treatment resistant strains of *Schistosoma* parasites, which have developed as a consequence of PZQ being the predominant treatment method for decades in regions of with endemic rates of schistosomiasis (Ismail M., et al, 1999; Fallon P. G., et al, 1995).

The ability of PZQ to control intracellular Ca\(^{2+}\) concentration also makes it a useful tool in the manipulation of cell signaling pathways in studies regarding the differentiation of anterior and posterior axes in planarian regeneration, another ongoing project in Dr. Marchant’s laboratory (Gurley K.A., et al, 2008). Achieving a better understanding of this property in a model such as the planarian will allow us to address such questions regarding cell differentiation in humans such as stem cell development and tissue regeneration.

My project will be studying the flatworm *Dugesia Japonica* as a model organism, as it expresses the same variant β-subunit as the genus *Schistosoma* yet lacks the potential health hazards inherent with the use of an infectious, parasitic model. Working with Dr. Nogi and Dr. Marchant, I will first develop an RNAi treatment to reduce expression of the variant β-subunit in planarian fed a bacterial vector. The treated worms will then be
exposed to PZQ at various concentrations. The resulting mortality data will give the 50% effective concentration (EC$_{50}$) value of the drug in RNAi treated planarian, which will be evaluated against that of the untreated control group. Given our hypothesis and the results of preliminary data collected so far, we expect to see an elevated EC$_{50}$ in planarian given the RNAi treatment compared to that of the control groups.

In our experiments we will also observe the effectiveness of the two enantiomers of PZQ (Figure 1), the (R)-form of which is believed to be active and the (S)-form inert. Specifically, we will observe whether the EC$_{50}$ of the optically pure (R)-form is half that of racemic treatments.

My experiments will be continuously adjusted based on the results of various treatments and the collaborative feedback I receive at weekly lab meetings, ensuring that my research is directed towards the overall objectives of Dr. Marchant’s laboratory. Upon the conclusion of my research, the results of my work will be presented either at an undergraduate research symposium or in a thesis written in the style of a publishable manuscript. Identifying the active site of PZQ in the genus Schistosoma will assist in the development of more diverse and effective drug treatments as well allow scientists to better address the increasing prevalence of treatment resistant strains of schistosomiasis.

**Figure 1. Praziquantel enantiomers**

(Left) (R)-PZQ  
(Right) (S)-PZQ