CCA iGEM Environmental Analysis
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Introduction:

Schistosomiasis (Bilharzia) is an infectious disease caused by parasitic flatworms and is prevalent in numerous tropical locations worldwide. Schistosomiasis-inducing flatworms undergo diagnostic and infective phases in their life cycle. During their diagnostic stage, flatworm eggs hatch into miracidia, which penetrate into freshwater snails. There, the miracidia develop into sporocysts that divide and form cercariae. Cercariae release into bodies of water marks the beginning of the infective phase, where they can penetrate human skin, circulate through blood, and mature into worms in the liver. The adult worms can then pair and release eggs via urine and manure. Eggs which remain within humans, however, can cause chronic bodily effects ranging from mild symptoms such as a rash or headache to severe ones such as organ inflammation, excretory issues, stunted mental and physical growth, and in rare cases, paralysis.

Despite the concerning effects of schistosomiasis and its wide impact, with 230 million infected and 700 million potentially at risk, it is considered to be a *neglected tropical disease* or *NTD,* a class of diseases which primarily affect the impoverished at a large-scale and whose research and prevention are not well funded.

Current Treatments:

Praziquantel is the usual treatment for Schistosomiasis, and is commonly paired with chemotherapy to function. This cure is taken in doses and proven to be most effective when used on grown worms, with cure rates between 65-90% after the initial dose. Despite these facts, Praziquantel is not flawless. It has shown to be not very effective or even harmful to young children and the elderly. Possible effects of Praziquantel include heart rhythm problems as well as conditions like peeling skin, fever, and stomach pain. An alternative and more efficient way of battling Schistosomiasis can be implemented by using yeast. By curing the snails, schistosomiasis is prevented as the snails cannot nurture the infecting worms. Using yeast on the snails prevents the problem from even happening (by curing the snail) which is more effective than just curing patients who have already contracted the disease.

Project Description:

We plan to contribute to the eradication of Schistosomiasis by targeting their intermediary host, snails. By curing the snails of Schistosoma, it loses a necessary stage in its life cycle, and thus miracidia doesn't transfer into worms, and therefore does not attach itself to human beings. To do so, we will genetically modify S.Cerevisiae yeast to produce sanguinarine within cell walls, and place it on the shores of Schistosoma-infected waters. Yeast naturally attracts snails from as far as 180 meters away, providing incentive for snails to consume yeast. The enzymes inside the snail guts will lyse or crack open the yeast cells. This releases built-up sanguinarine, a substance proven to kill Schistosome miracidia. As this substance is absorbed and carried throughout the bloodstream, the snail is cured.

Ecological Role of Snails:

Biomphalaria glabrata are the freshwater snail species that host the parasitic worm that cause human schistosomiasis. The worm lives in its larvae stages inside the snail before it completes its life cycle, so the Biomphalaria glabrata is crucial in order for the trematode to survive.

Snails are mollusks, which appear on all continents but are most prominent in Eastern North America. Their diet consists mainly of plants, rotting wood, fungi, algae, and other organic matter. Through their diet they consume calcium, which they concentrate into their shells that are made from calcium carbonate. They then pass this calcium up the food chain when they are consumed by larger predators. Because of this, they are a very important source of food for predators such as birds, insect larvae, mice, amphibians, and other small mammals. Additionally, the slime secreted by the snails as they move is beneficial to the soil underneath, improving its structure. Their diet also aids with the quality of the soil, as they decompose decaying plant matter, leaving behind nutrient-rich feces.

Freshwater snails, a type of snail typically found to carry Schistosomiasis, are actually otherwise extremely beneficial to the environment. They keep the waters of their habitat clean and in good conditions. Snails consume algae using a feeding mechanism in their bodies, called a radula. A radula is an organ with a bunch of tiny, teeth-like scraping tools. This algae consumption reduces the chances of algae smothering other plant species, and prevents the reduction of nutrient levels in bodies of water. It also balances the pH of the water, which is necessary to many other plants' survival. The death of freshwater snails is also beneficial to the environment. Bizarrely, in a kind of regulatory system, the decomposition of their bodies lowers the pH of the waters, but the decomposition of their shells raises it. Of course, many other species of animals consume the snails as sustenance, making them one of the most common sources of food in their environments

Because we're aware of the important role of these snails in their ecosystems, we're aiming to use an approach that won't harm them. We chose to use sanguinarine, a selectively toxic compound, to target the schistosomes in the snails. When parasites infect snails, the larva, also called miracidia, undergoes a dramatic morphological transformation into a contained, cyst-like structure called a primary sporocyst, which travels to and initially develops in the hepatopancreas (digestive gland) of the snail. We are targeting the sporocyst intermediate stage of the schistosomes' development, and therefore are aiming to have sanguinarine travel to the hepatopancreas. The snail is unlikely to fully digest the compound in the digestive tract, which means that it itself will not die while being cured.

Safety of Releasing Yeast (or other GMOs) into Environment:
Similarly to most synthetic biology research, our project takes advantage of genetically modified organisms (GMOs) for our solution. Specifically, we plan to genetically engineer yeast to express sanguinarine. Since the final implementation of our project involves introducing genetically modified yeast into the environment—albeit in a contained manner—we must thoroughly examine the potential biosafety risks and choose the safest approach accordingly.

The majority of GMOs can efficiently reproduce, multiply, and spread once they are released into the environment, as the genetic modifications of the organism give it a selective advantage in survival. There is often an increased pressure placed on native populations, which are unable to quickly adapt to the presence of a new invasive species. The danger a GMO poses on the environment varies depending on its characteristics, interactions between other organisms and its surroundings, genetically modified traits, and the environment itself. Introducing a GMO to an environment could have unexpected and hazardous consequences due to the unpredictability of the changes in the organism's growth rate, metabolism, evolutionary pattern, and response to external environmental factors.

Because of the aforementioned variability in the environmental harms caused by GMOs, we examined in-depth the environmental changes caused by baker's yeast, formally known as S. cerevisiae, which is the strain we are using for our project. When genetically modified (GM) yeast strains were placed into a simulated environment containing indigenous microorganisms, there was minimal disruption in the viability of indigenous microorganisms (Ando et. al, 2009). The same results were noticed in aquatic environments. In fact, the survivability of the GM yeast was either the same or lower than that of wildtype yeast strains (Ando et. al, 2005). These results strongly suggest that the accidental or intentional release of GM yeast strains will not have an effect on microbial communities, making yeast a safer option for our project compared to other organisms.

Of course, these findings should not be misconstrued to suggest that the unregulated release of yeast into the environment will have no impact at all. There is still minimal research into the possibility of horizontal gene transfer between GM yeast and other organisms. Additionally, it has been observed that indigenous microbial communities may use nutrients derived from the dead yeast cells, so further research is required into the long-term environmental changes that may occur.

The most effective method to minimize the release of any GM yeast into the environment is “contained use,” so our team plans to cultivate the yeast in a contained bioreactor without any direct contact between the external environment and the yeast.