Marine Compounds Against Drug Resistant *Plasmodium*

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Background

The term malaria in Italian means 'bad air', coined through its association with marshy areas (Tuteja, 2007). Malaria has been a problem for more then 4,000 years and to this day we still struggle to fight it off, with 40% of the world's population living in endemic countries (Malaria, 2012; Sullivan, Kaludov, & Martinov, n.d.). The first medicinal remedy utilized against malaria was Quinine, found in the bark of the Cinchona tree (Wells, 2011). Later around 1971, it was synthesized as Mefloquine (Wells, 2011). There have been many other novel antimalarial drugs developed from natural compounds, such as Artemisinin derived from wormwood and developed in 1971 (Wells, 2011). Due to the repeated use of the available antimalarial drugs over an extended period of time, the *Plasmodium* strains have developed a resistance to various drugs (Ginsburg & Deharo, 2011). With malaria being one of the most deadly and dangerous diseases, there is a high need for new drug development (Guantai, & Chibalea, 2011).

Design/Method

This study will take 100 marine fractures and test them against drug resistant strain of *plasmodium falciparium* for viable antimalarial drugs. The marine fractures acquired from HBOI are aliquoted in various serial dilutions (.01, .1, 1, 10 micrograms/milliliter) containing drug resistant *plasmodium falciparium* infected red blood cells in phenol red free media (Plouffe, Brinker, McNamara, Henson, Kato, Kuhen, & ... Winzeler, 2008; R. Bracken, personal communication, February 7, 2013). Utilizing 1 millimolar of Cloriquine as the positive control and an uninfected culture for the negative control and the serial dilutions of the marine fractures to create an IC_{50} curve utilizing the program Prism from graph pad. If the serial dilution of 1 micrograms/milliliter or less passes the IC_{50} test the compound is then tested for cytotoxicity (how toxic the compound is the human body). Cytotoxicity is determined using fibroblast cells (they are the cells that make up the connective tissue throughout the body) to test serial dilutions of the marine compound fractures in fibroblast cell media. The fibroblast cells are treated with varying concentrations of compound and then read MTS assay (cell viability assay) using a cell titer glo by promega (Poluffe et al., 2008; R. Bracken, personal communication, February 7, 2013). If these tests are passed the fracture is a good candidate for animal trials. A marine fracture may pass the cytotoxicity test but fail at animal trials due to only fibroblast cells being tested. If successful in animal trials it can be presented for human trials and drug approval.

Results

On average natural product fractions have a higher hit rate then synthetic compounds about a 10% hit rate compared to 1% hit rate of synthetic compounds (R. Bracken, personal communication, February 7, 2013). Out of the 10% that have passing IC_{50} levels only about 1-2% will have expectable therapeutic windows (R. Bracken, personal communication, February 7, 2013). This is the point where it kills off the *Plasmodium falciparium* while still being safe for human use. This selectivity index is determined by dividing the cytotoxicity value by the IC_{50} value (R. Bracken, personal communication, February 7, 2013). A selectivity index level of 10 or higher will only be considered fore drug approval (R. Bracken, personal communication, February 7, 2013). The selectivity index is highly important with malaria due to malaria effecting 85% of children under five years of age (Wells, 2011). So only 1 to 2 fractions out of the 100 will be viable drugs and even those hits still need to have the active fraction isolated (find out what is directly effecting the virus for possible synthesizing of the fraction).