Repurposing Farnesyl Transferase Inhibitors for the Treatment of Cerebral Malaria

First-in-class treatment of cerebral malaria by preventing the pathological loss of the blood-brain barrier.

Technology

The Rodriguez research group has discovered a novel application for Farnesyl Transferase inhibitors tipifarnib and lonafarnib in treating cerebral malaria. Currently used as therapeutic inhibitors of the isoprenoid synthesis pathway, tipifarnib and lonafarnib are FDA approved for the treatment of cancer and progeria in children, respectively. The Rodriguez group demonstrated for the first time that these pharmacological Farnesyl Transferase inhibitors also protect against the disruption to the blood-brain barrier (BBB), which is the underlying cause of cerebral malaria mortality. Specifically, in human brain microvascular endothelial cells, tipifarnib and lonafarnib showed complete or partial protective effects respectively, from *P. falciparum*-induced disruption to the endothelial barrier. Additionally, in an *in vivo* model of cerebral malaria, tipifarnib treatment resulted in a significant decrease in both mortality and neurological impairment in infected mice. These compelling findings represent the first to identify a therapeutic that addresses the underlying cause of cerebral malaria mortality.

Background

Malaria causes approximately 247 million clinical episodes per year, between two and four million cases of severe disease, and 619,000 estimated deaths. Despite renewed efforts to eradicate malaria, it remains a major cause of global death and disability. Cerebral malaria is a life-threatening complication of severe malaria, affecting about 2% of malaria patients. After the first neurological symptoms appear, cerebral malaria has a rapid onset reaching a mortality rate of 15% within 48 hours. The disease is characterized by the loss of brain endothelial cell junctions and the disruption of the BBB caused by erythrocytes infected with the etiological agent of Malaria, the *Plasmodium sp*. parasite. Currently, there are no specific treatments for cerebral malaria and clinicians can only treat with classical antiparasitic drugs to eliminate the parasite before extensive loss of the BBB integrity causes death. Accordingly, there remains a need for a treatment that targets the rapid loss of the BBB integrity during cerebral malaria which would extend the currently narrow therapeutic window of classical antiparasitic drugs.

Application

- Treatment of the underlying pathology of cerebral malaria.
- Potential treatment for pathological endothelial disruption caused by other infectious diseases, such as Flu, Ebola, COVID-19, or Dengue viral infections.

Advantages

Technology ID

ROD01-17

Category

Doug Brawley

Life Sciences/Therapeutics/Antiparasi

Life Sciences/Therapeutics/Infectious Disease/Malaria

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- **First-in-class:** Targets the isoprenoid synthesis pathway to protect brain endothelial cells, which in not the target of any cerebral malaria therapeutic.
- **Clinically safe:** Tipifarnib and lonafarnib have already been demonstrated to be safe in humans.
- **Accelerated development pathway:** Both tipifarnib and lonafarnib are FDA-approved drugs, allowing for accelerated 505(b)(2) FDA regulatory approval and clinical translation.

Intellectual Property

NYU has filed a provisional patent application covering method of use.