The Anti-Parasitic Drug Atovaquone Inhibits Arbovirus Replication

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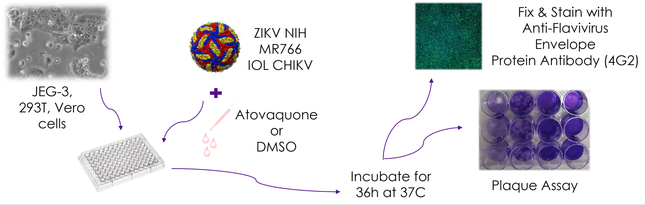
ABSTRACT

Arboviruses are an emerging public health threat yet currently there are limited vaccines and no effective antiviral therapies targeting these pathogens. Recent outbreaks of Zika virus (ZIKV) in the Americas have highlighted the urgent need to develop these antivirals to treat at-risk populations such as pregnant women and children. One avenue for anti-arbovirus drug development is to repurpose known, approved, and pregnancy-friendly drugs that have antiviral potential to be used on these vulnerable individuals. We addressed the antiviral activity of several pregnancy-friendly drugs as well as known antiviral compounds. Interestingly, we found that Atovaquone, a hydroxynaphthoquinone, FDA Pregnancy Category C drug used for the treatment and prevention of *Pneumocysits jirovecii* pneumonia (PCP) and parasitic infections such as malaria inhibited ZIKV and chikungunya virus (CHIKV) replication *in vitro*. To date, antiviral activity of this drug has not been described. We proposed Atovaquone as a potential anti Zika virus (ZIKV) candidate given its structural proximity to ubiquinone (Coenzyme Q) and therefore active role in *de novo* pyrimidine synthesis.

PURPOSE

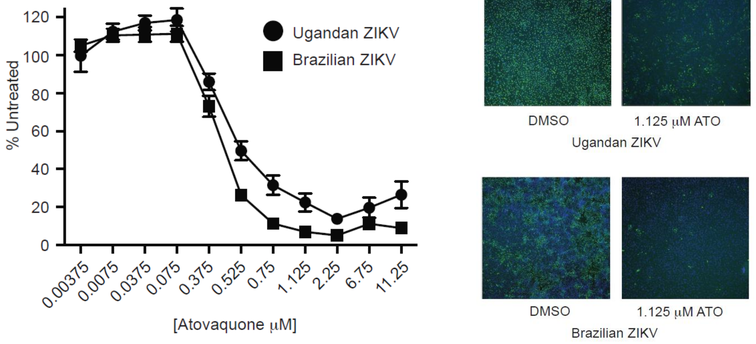
- To find anti-Zika virus activity in "pregnancy-friendly" existent drugs.

METHODS

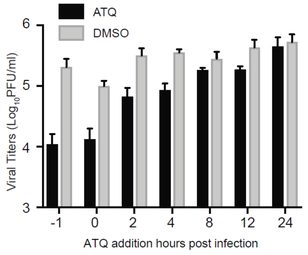


RESULTS

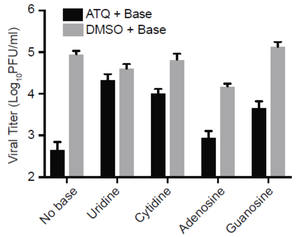
Atovaquone inhibits ZIKV



Atovaquone inhibits ZIKV at early stages of viral cycle

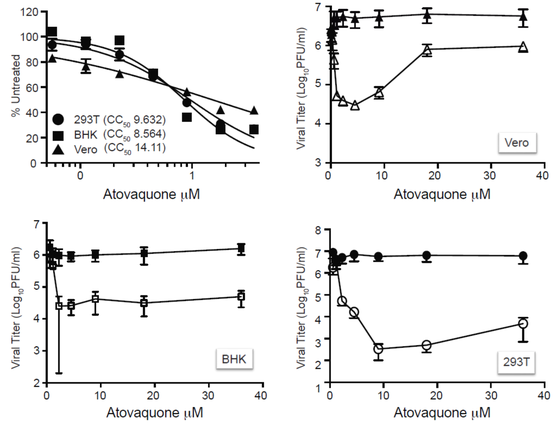


Uridine rescues ZIKV infection

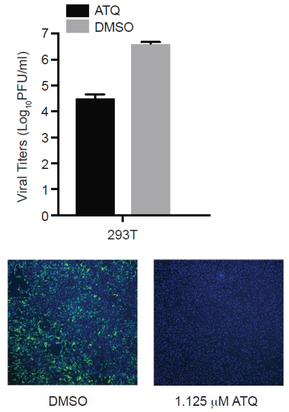


RESULTS

Atovaquone inhibits Zika virion production in animal & human cells



Atovaquone inhibits CHIKV



CONCLUSIONS

- Our findings reveal that **Atovaquone has antiviral activity against ZIKV and CHIKV** and this has the potential to be translated in the clinical setting into an attractive candidate for the treatment of arbovirus infections in vulnerable populations such as pregnant women and children.
- In addition to its role in inhibiting mitochondrial membrane potential, **Atovaquone likely inhibits pyrimidine biosynthesis** by competing with ubiquinone (Coenzyme Q) which is a substrate of DHO dehydrogenase enzyme, functioning through the depletion of cellular nucleotides.
- Studies are underway to address this mechanism and to determine the potential broad-spectrum antiviral activity of Atovaquone *in vitro* and *in vivo*.

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