

## **ACCELERATED DISCOVERY AND DEVELOPMENT OF RE-PURPOSED LICENSED DRUGS FOR ZIKA VIRUS OUTBREAK ANTIVIRAL PROPHYLAXIS AND THERAPY**

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**Purpose:** A combination of mechanism-based drug selection and robotic-based high throughput screening has tested and identified re-purposed drugs suitable for clinical development for Zika virus antiviral medical countermeasures. Clinical trials have been developed for lead candidates. The strategy and process employed has been developed in response to the limited timeframe available to reduce the morbidity and mortality associated with the initial wave of ZIKV infectious outbreak spread.

**Methods and Materials:** A combination of mechanism-based drug selection and robotic-based high throughput screening has been employed to rapidly select active drug compounds. Compounds screened are already approved for other indications by the FDA, so the process for FDA approval for other indications, such as use as an antiviral for the Zika virus is abbreviated.

Drug activity was tested in a range of cultured cell types and primary human cells, both as single agents and as drug combinations. Testing has been performed using multiple Zika virus isolates. Individual drug candidates were selected based on known mechanism(s) of action consistent with inhibition of Zika virus replication, measured inhibitory concentrations, and human safety profile at currently recommended clinical dosage. Population pharmacokinetic modeling was used to select compounds based on a combination of antiviral activity and likely bioavailability at known safe dosing levels. To define the anti-Zika viral inhibition effectiveness required for use in community-based outbreak containment, intervention effectiveness modeling was performed. Results were used to define a target product profile, animal trials are ongoing and corresponding clinical development and testing strategies begun.

**Results:** Re-purposed drug selection employing hypothesis-driven high throughput screening, combined with population pharmacokinetic modeling, has succeeded in identifying Zika virus prophylactic and therapeutic medical countermeasure candidates; efficacy required to support ring containment of Zika virus outbreaks has been modeled, strategies for efficient clinical testing and development of identified

compounds have been prepared, and the drug candidates are ready for advanced development. Planning for clinical trials is underway.

**Conclusion:** This research has been performed with quality by design drug development principals, the drug candidates are now in expedited animal model screening, and clinical testing is ready to commence. In a broader context, a successful strategy and process for rapidly identifying re-purposed drug candidates for treatment and prevention of other emerging viral pathogens has been developed.