Team tackles equine encephalitis viruses

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The UW-Madison School of Pharmacy is located in Rennebohm Hall. Credit: UW-Madison

Viruses without a preventative vaccine or treatment option pose a looming threat. But for viruses in this category that have already been weaponized and are recognized as human biothreats by the Centers for Disease Control and Prevention, it's a race to find a cure.

For equine encephalitis viruses, or EEVs, this scenario is made more dire in that the viruses infect humans through the bite of an infected mosquito. With no drugs approved by the Food and Drug Administration for human use against these pathogens, the human population is at risk. EEV infection in people can manifest as relatively mild flu-like symptoms or can progress to neurological impairment, seizures or death. The most severe of the three EEVs, Eastern equine encephalitis virus, has been diagnosed in at least 20 states, including Wisconsin, and has a mortality rate of greater than 50 percent.

"We've made a breakthrough in creating new small molecules that penetrate into the brain where the virus resides and interfere with viral replication to stop EEV," says Jennifer Golden, a professor of pharmaceutical sciences and associate director of the Medicinal Chemistry Center at the University of Wisconsin-Madison School of Pharmacy.

In a study published in *Antiviral Research* this month, Golden and her collaborators show that all of the mice treated with one compound developed in the Golden lab at the School of Pharmacy survived when exposed to a lethal EEV.

"Remarkably, we also show that delaying treatment for 48 hours to mice that are already infected still results in 90 percent survival. Now we're working to better resolve the mechanism behind the antiviral effects that we observe, along with compound characteristics that must be understood, before a compound can be developed into a drug," says Golden.

Golden is one of three principal investigators on a multidisciplinary research team whose work is funded by a new, five-year, $21 million award from the National Institutes of Health. The NIH funding establishes a new Center of Excellence for Encephalitic Alphavirus

Therapeutics, which will support the preclinical development of small molecules to treat EEVs.

"The goal of this new grant is to develop a safe and effective broad-spectrum antiviral through preclinical assessment to clinical candidacy for FDA review before human clinical trials," says Golden.

One of the most difficult tasks for Golden and her research team is balancing features that make a molecule effective against EEVs but also safe for a patient. Pioneering chemistry that modifies the molecular structure to afford a compound that is both safe and effective takes persistence, experience and a coordinated effort between chemistry and biology.

"The UW-Madison School of Pharmacy is the engine of this important drug discovery work right here in Wisconsin, having the full capabilities to identify, design and develop novel compounds that will improve human health," says Steven Swanson, dean of the school. "It's no small feat to create new chemistry with this kind of complexity."

Golden's virology research collaborators in the new center include Colleen Jonsson at the University of Tennessee Health Science Center, and Donghoon Chung at the Louisville Center for Predictive Medicine. Golden, a medicinal chemist, is leading the design and synthesis of the antiviral compounds. Jonsson is implementing the animal efficacy and viral resistance studies, and Chung provides cellular and biochemical assays to evaluate cellular activity and determine how the compounds target the viruses.

With the establishment of the center of excellence, the interdisciplinary research team has assembled a world-class team of scientists with exceptional cross-disciplinary drug development and scientific expertise to optimize antiviral compounds that are effective for emerging EEV

viruses.

Provided by University of Wisconsin-Madison