Researchers discover target for treating Dengue fever

AURORA, Colo. (April 17, 2014) – Two recent papers by a University of Colorado School of Medicine researcher and colleagues may help scientists develop treatments or vaccines for Dengue fever, West Nile virus, Yellow fever, Japanese encephalitis and other disease-causing flaviviruses.

Jeffrey S. Kieft, PhD, associate professor of biochemistry and molecular genetics at the School of Medicine and an early career scientist with the Howard Hughes Medical Institute, and colleagues recently published articles in the scholarly journals eLife and Science that explain how flaviviruses produce a unique RNA molecule that leads to disease.

More than 40 percent of people around the world are at risk of being bitten by mosquitoes infected with the virus that causes Dengue fever and more than 100 million people are infected, according to eLife. Many develop headaches, pain and fever, but some develop a life-threatening condition where tiny blood vessels in the body begin to leak. Other flaviviruses, such as West Nile virus, are rapidly spreading around the globe. Flaviviruses are considered dangerous emerging pathogens.

The eLife paper shows that the virus causing Dengue fever and other closely related viruses like West Nile and Japanese encephalitis use instructions encoded on a single strand of RNA to take over an infected cell and reproduce. The viruses also exploit an enzyme that cells use to destroy RNA to instead produce short stretches of RNA that, among other things, may help the virus avoid the immune system of its host. Ironically, these viruses use a structured RNA molecule to resist an enzyme that normally "chews up" RNA.

The Science paper reveals the discovery that the resistant RNA folds up into an unprecedented "knot-like" structure. The enzyme, normally adept at breaking up RNA structure, encounters this particular structured RNA and cannot "untangle" it; thus the enzyme is thwarted. This is the first time this sort of RNA structure has been observed and it has characteristics that may be amenable to targeting by new drugs. To discover this structure, the researchers used a technique called x-ray crystallography, which allowed them to determine the structures of individual molecules.

This understanding of how an RNA found in many different flaviviruses thwarts a powerful enzyme may help scientists develop treatments or vaccines.

Kieft is the corresponding author of the eLife aticle. The other authors are Erich G. Chapman, PhD, Stephanie L. Moon and Jeffrey Wilusz, PhD, professor of microbiology, immunology and pathology at Colorado State University. Kieft is also the corresponding author of the Science aticle. The other authors on the Science article are Chapman, David A. Costantino, MS, Jay C. Nix, PhD, Moon, and Wilusz. Funding was provided by the Howard Hughes Medical Institute and the National Institutes of Health

Faculty at the University of Colorado School of Medicine work to advance science and improve care. These faculty members include physicians, educators and scientists at University of

Colorado Hospital, Children's Hospital Colorado, Denver Health, National Jewish Health, and the Denver Veterans Affairs Medical Center. The school is located on the Anschutz Medical Campus, one of four campuses in the University of Colorado system. To learn more about the medical school's care, education, research and community engagement, visit its web site.