Quick screening method identifies promising anti-Ebola drugs

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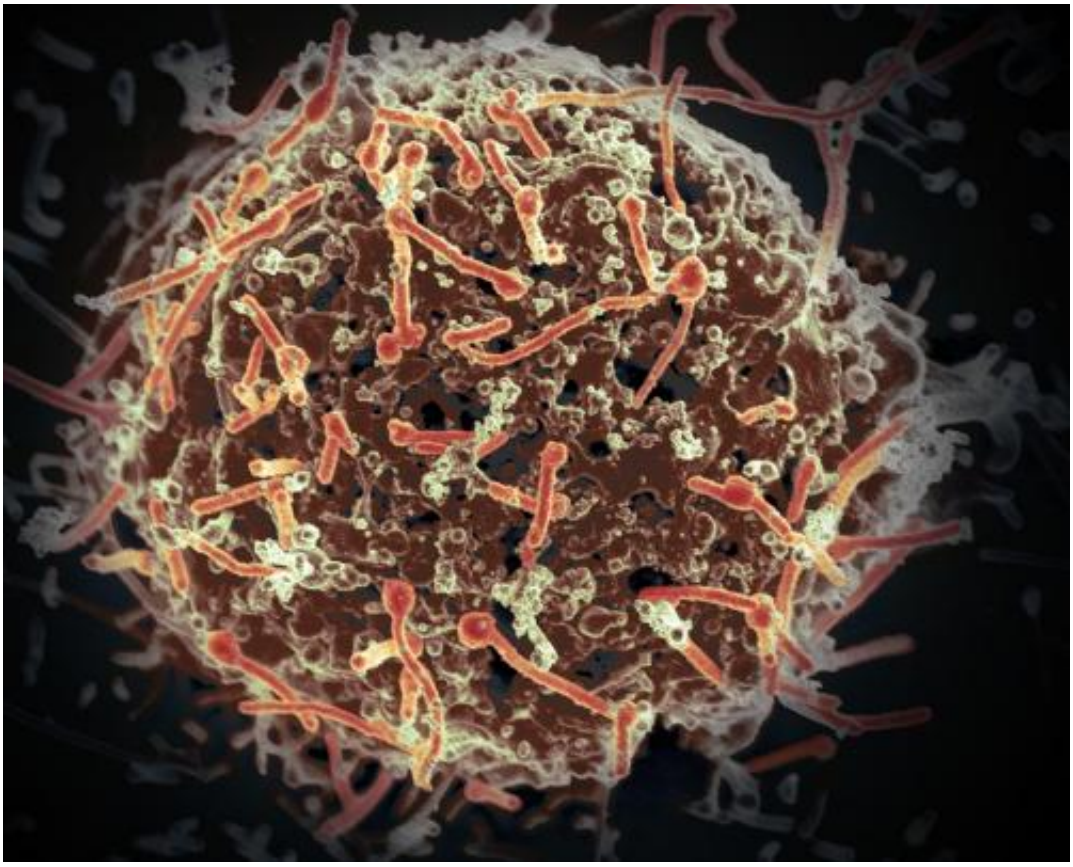

The Ebola virus, isolated in November 2014 from patient blood samples obtained in Mali. The virus was isolated on Vero cells in a BSL-4 suite at Rocky Mountain Laboratories. Credit: NIAID

A quick screening method has been used for the first time in a standard open laboratory to identify and test promising anti-Ebola drugs. This

approach increases the possibility of finding new therapies faster.

A team from the Toronto General Research Institute, University of Toronto, Canadian Blood Services, the National Microbiology Laboratory in Winnipeg and the U.S. National Institutes of Health used a mini-genome system to rapidly evaluate candidate drugs that could inhibit the Ebola virus. The team was led by Dr. Eleanor Fish, senior scientist in the Toronto General Research Institute (TGRI) and Dr. Donald Branch, senior scientist in the Centre for Innovation - Canadian Blood Services and TGRI.

Their results, published today in *PLOS Neglected Tropical Diseases*, provide details on the procedure for evaluating candidate anti-Ebola drugs and comparing the antiviral effectiveness of eight drugs from three different drug classes. Interferons and anti-HIV drugs showed antiviral activity against the Ebola virus in their studies.

To date, no vaccines, treatments, or post-exposure prophylaxis are available for Ebola.

The screening procedure - used in the U.S. to model and study virus replication - allows for continuing evaluation of new antivirals or anti-Ebola drugs, since there is a likelihood of future Ebola outbreaks. This is the first time this method has been used to test anti-Ebola drugs.

Research on new Ebola therapies has been limited by an inability to compare antiviral effectiveness, since cell model systems, treatment regimens and results are so varied that it is difficult to compare effectiveness amongst the compounds, and prioritize which ones are most promising to pursue.

"During this recent Ebola outbreak it became clear that many different experimental drugs were being considered, yet studies to evaluate the

effectiveness of candidate drugs are hampered by the limited availability of appropriate safety level labs around the world and the difficulty of comparing results when different model systems were being used, said Dr. Fish. "Prioritizing drugs for further pre-clinical evaluation was difficult."

The method and technology used for this study can be performed in most labs and evaluation of two and three drug combinations can also be examined using this method.

"We tested combinations because lower doses of each drug can be used, potentially decreasing side effects," said Dr. Fish, a Professor in the Department of Immunology at the University of Toronto. "Using this technology, scientists will be able to measure the inhibitory effects of their experimental drugs on the replication of Ebola virus, allowing us to compare results with confidence. This approach will also decrease the possibility of the emergence of drug resistance."

The team's results were validated using fully infectious Ebola virus in the Level 4 lab in Winnipeg.

Hemorrhagic fevers like Ebola have a high mortality rate and are transmitted from human to human by infectious body fluids. For these reasons, experiments with the Ebola virus are always performed in laboratories with maximum protection and containment - a biosafety Level 4 Laboratory - which has limited the number of labs that can perform antiviral studies.

Because the Ebola virus-like particles used for screening different drugs in this study were not fully infectious, Level 4 was not required.The viral mini-genome generated modifies the Ebola virus to produce virus-like particles that are no longer harmful to humans. The researchers were therefore able to do their work in a biosafety Level 2 Laboratory, which

only requires some enhanced measures such as gloves and biological safety cabinets.

Using human cells and this model infection system, the researchers compared how well eight different drugs, in different combinations, at different doses and at times post-exposure, were able to inhibit the virus. Interferon beta, the most potent inhibitor of Ebola which the team identified as a result of the screening, is now part of a clinical trial of individuals who were infected with Ebola during the recent outbreak in Guinea.

"It was found that drugs normally used to treat HIV/AIDS were also effective at inhibiting Ebola, alone, but more so in combination with interferon beta," noted Dr. Branch, who is also an Associate Professor, Medicine and Laboratory Medicine and Pathobiology, University of Toronto.

As of December 20th 2015, 28,637 cases and 11,315 deaths from Ebola have been reported worldwide, the vast majority of them in West Africa. The high mortality rate of the disease, estimated at around 60% in the most recent outbreak, made it one of the most deadly infectious diseases in the world. The World Health Organization (WHO) declared the outbreak in 2014-15 a public health emergency of international concern and it is the largest outbreak to date.

At this time, no confirmed cases of Ebola were reported in the week to January 3, 2016. Guinea, Liberia, and Sierra Leone have all now succeeded in stopping human-to-human transmission linked to the original outbreak in West Africa. Outbreaks occur intermittently in tropical regions of sub-Saharan Africa.

Provided by University Health Network