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Using Drug Repurposing as Host-Oriented Therapies to Treat Ebola Infections

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Introduction

Ebola virus is a human pathogen that causes the rare Ebola virus disease (EVD), with Zaire ebolavirus (ZEBOV) species being the most dangerous of the known EVD-causing viruses, causing 90% mortality rates. Ebola virus exhibits a person-to-person transmission through body fluids and oral exposure, and was found to remain viable and transmissible in eye, semen, amniotic fluid, the placenta, breast milk and the central nervous system for at least 6 months [1].

Although the outbreaks of Ebola are sporadic, the Ebola virus is an aggressive and deadly pathogen. The latest and still not completely contained 2014-2015 Ebola epidemic is the largest outbreak in human history, which affects multiple countries in West Africa [2]. As of October 26, 2015 there are 15,211 confirmed total cases including: 3,350 in Guinea, 3,151 in Liberia and 8,704 in Sierra Leone, according to WHO data.

Currently, there are no licensed drug treatments or broadly active vaccines available to treat Ebola. Several experimental antiviral therapies have been used with mixed success to treat patients with EVD during the most recent Ebola outbreak. Below is the overview of the current experimental antiviral therapies.

Vaccines against Ebola

Vaccination remains one of the forms for possible protection against the viral infection. Although it is generally used as a preventative measure, there are a number of vaccines with various degrees of effectiveness that are being developed, and which could be used as a means of therapy to treat already infected individuals.

An additional potential treatment option was developed by scientists at the National Microbiology Laboratory in Winnipeg, Canada and is currently in clinical trial stage. Vesicular Stomatitis Virus-Ebola Virus vaccine or VSV-ZEBOV vaccine contains an attenuated livestock virus engineered to produce an Ebola protein [3]. The vaccine was shown to be 75-100% effective for a period of three weeks, which generally corresponds to the duration of an outbreak. Further studies need to be conducted in order to confirm whether the vaccine offers longer time protection or not. However, there are limitations to the uses of such a vaccine, as it must be stored at -80°C and it offers protection against only a limited number of the Ebola virus species.

Pathogen-Oriented Therapy against Ebola

Currently, there are a number of interventions available as promising pathogen-oriented treatments against the Ebola virus. One of them is ZMAb, a monoclonal antibody that has been shown to protect two out of four nonhuman primates when administered 2 days post-infection (dpi) [4-6]. When this monoclonal antibody treatment was combined with adenovirus-vectored interferon-α preparation, this combination of treatments showed 75-100% survival when treated 3 dpi (depending on macaque species used).

Host-Oriented Treatments against Ebola Infections

Besides vaccinations and pathogen-directed therapies, there are a number of other treatment options that are being developed, including the use of host-oriented anti-Ebola drugs. A number of compounds have been found to target and inhibit various processes of Ebola Virus infection mechanisms. For example, through screening a library of small molecules, Cote et al. have identified a novel benzylpiperazine adamantine diamide-derived compound that was shown to inhibit EBOV infection through prevention of EBOV entry [7]. Sakirai et al. showed that tetrandrine, a compound originally isolated form Chinese and

Japanese herb, can inhibit infection of the primary target of Ebola virus, human macrophages [8].

Drug Repurposing as Ebola Countermeasures

Due to the pressing nature of Ebola treatments, a number of scientists concentrated their efforts on the testing of drugs previously approved by U.S. Food and Drug Administration (FDA), which have been used for other indications to treat Ebola infection. Such drugs already have well-established safety and pharmacokinetic profiles in patients, and thus can be repurposed for new disease indications. Drug repurposing has gained a growing interest in various fields of research. In the past couple of years, there has been an observed outburst of drug repurposing efforts against biological threat agents, including Ebola [9-12].

One such example can be seen in the Madrid et al. paper, where the authors have identified a number of compounds, including chloroquine, an antimalarial drug, to have an effect on the entry and replication of two tested types of EBOV in vitro, and showed protection in mice against the virus [9]. On the other hand, Kouznetsova et al. have developed a robust high throughput screen, and has identified 53 FDA-approved lead compounds that could potentially be developed as therapies against Ebola virus infections [11]. Johansen et al. additionally discovered 80 FDA-approved drugs to offer protection against in vivo murine Ebola virus. These authors have also showed a mechanism of action of a number of the drugs including sertraline (Zoloft), a selective serotonin reuptake inhibitor, and bepridil (Vascor), a calcium channel blocker in inhibiting a late stage of viral entry [12].

While all of the above-mentioned repurposing studies were targeting viral proteins, Zilbermintz et al. technology was aimed on discovery of host-oriented therapies [10]. Host-oriented therapies offer advantages over the conventional pathogen-directed therapies in that the use of treatments is targeted at the host, and does not result in pathogen developing resistance against the treatment. The authors have designed a cell-based multiplex approach to screen a library of FDA-approved drugs. The group is based at Keck Graduate Institute, Claremont, California. The study published in Nature Scientific Reports describes a collaborative effort with Stanford University, UCLA and USAMRIID. The authors illustrated the broad antipathogenic actions of an antimalarial drug, amodiaquine (AQ, a compound structurally similar to chloroquine, but exhibiting more potent and more stable activity) and its metabolite desethyl-amodiaquine. The authors have also showed the mechanism of AQ action to control ZEBOV infection through the ability of the drug to interfere with the functioning of the host protein, cathepsin B. AQ is currently used in West Africa as antimalarial treatment as well as a prophylaxis. The results of the Zilbermintz et al. study were conveyed to the Doctors without Borders who observed that the administration of AQ provided a substantial protection against Ebola and reduced the Ebola-caused mortality by 31% [13].

Host-oriented therapies in infectious diseases could either work as a monotherapy or as a combination therapy when coupled with pathogen-oriented drugs. Host-oriented therapy is directed against the host and does not kill the pathogen. This might result in re-emergence of infection and might cause life-threatening complications. Therefore, a combinatorial therapy would be an obvious choice to prevent re-emergence of infection as in recently published case of Pauline Cafferkey, a Scottish nurse who initially recovered from Ebola, but then suffered relapsing infection, causing life-threatening meningitis [14].

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