Commentary

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Drug development for controlling Ebola epidemic – A race against time

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Summary **The Ebola outbreak in West Africa this year is causing global panic. The high mortality of this disease is largely due to lack of effective preventive vaccines or therapeutic drugs. Realizing the gravity and urgency in controlling the epidemic, governments and drug companies across the world have taken many strong measures to speed up the process of drug development. Several representative candidate drugs that demonstrate potent anti-Ebola activity in preclinical studies have been pushed forward to higher research stages to obtain an earlier official license. It is expected that proven preventive or therapeutic regimens could be established in the near future.**

Keywords: Africa, vaccine, ZMapp, TKM-Ebola, jk-05

The Ebola outbreak identified in Guinea in March this year is currently getting worse across the world. According to the statistics of World Health Organization (WHO), a total of 9,216 confirmed, probable, and suspected cases of Ebola virus disease (EVD) and 4,555 deaths have been reported in seven affected countries including Guinea, Liberia, Nigeria, Senegal, Sierra Leone, Spain, and the United States of America up to the end of 14 October, 2014 (*1*). It was predicted by WHO that the number of patients and deaths might continue increasing from hundreds to thousands per week in the coming months if control measures are not significantly improved (*2*). Facing such a grim situation, an alarming fact is that there are no proven therapies or vaccines against this deadly disease. However, it is a comfort that this epidemic on the verge of being out of control has eventually caused comprehensive attention in the international society. Drug development for controlling the epidemic enters the speedway in the world.

ZMapp, an experimental drug developed by Mapp Biopharmaceutical (USA), is a combination of three humanized monoclonal antibodies that are produced in genetically modified tobacco plants (Table 1) (*3*). In preclinical studies, it provided a survival benefit in nonhuman primates that were experimentally infected with the virus (*4,5*). In addition, a recent study demonstrated that this drug was capable of rescuing rhesus macaques that had developed advanced EVD (*3*). Although it has never been tested in humans, the drug has been given to 7 patients with EVD on the basis of 'compassionate use', thus far. In these cases, 5 have survived and 2 have died. In the near future, the US government will provide funding, expertise, and technical support to Mapp Biopharmaceutical to accelerate the development of ZMapp. According to the signed contract of both parties, the government will provide the drug maker with an initial funding of US 24.9 million dollars over 18 months to support work toward acquiring US Food and Drug Administration (FDA) approval of the drug (*6*).

Another drug that has been recently approved by FDA for testing in Ebola patients is TKM-Ebola, a cocktail of small interfering RNA produced by Tekmira Pharmaceuticals, Canada (Table 1) (*7*). In a preclinical study, macaques were administered TKM-Ebola after Zaire Ebola virus challenge and the survival of animals was examined. Results demonstrated that 2 of 3 macaques were protected from lethal Ebola virus infection when given 4 postexposure treatments, whereas all 4 macaques were protected when given seven postexposure treatments (*8*). This study suggested that TKM-Ebola might be effective for people infected with Ebola virus. Unfortunately, during the phase I trial of this drug, it was observed that TKM-Ebola induced cytokine release in participants and thus had been put on clinical hold by FDA earlier this summer. However, in response to the Ebola outbreak in West Africa this year, the FDA consequently

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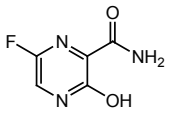
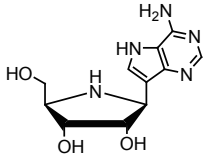
Table 1. Potential anti-Ebola drugs or vaccines in development

Agent	Structure/composition	Test species	Developer	*Ref.*
ZMapp	Monoclonal antibodies: c13C6, c2G4, and c4G7	Monkey; patients for compassionate use	Mapp Biopharmaceutical (USA)	*3*
TKM-Ebola	Small interfering RNAs	Monkey	Tekmira Pharmaceuticals (Canada)	*7*
jk-05	Small molecule compound	Animals	Academy of Military Sciences (China)	*9*
Favipiravir		Mouse	Toyama Chemical (Japan)	*10*
BCX4430		Monkey	BioCryst Pharmaceuticals (USA)	*13*
cAd3-ZEBOV	Vaccine	Phase I study	GlaxoSmithKline (UK)	*14*
VSV-EBOV	Vaccine	Phase I study	National Microbiology Laboratory (Canada)	*15*

modified its clinical hold to allow the drug company to propose studies in patients infected with the virus.

jk-05, a small molecule compound developed by Academy of Military Sciences (AMC) of China, has broad-spectrum antiviral activities and the phase I trial on its clinical safety has been completed (Table 1) (*9*). This drug is capable of inhibiting the RNA polymerase of Ebola virus selectively, resulting in a suppressing effect on virus replication. Studies demonstrated that jk-05 possesses antiviral activity against Ebola virus both *in vitro* and *in vivo* (*9*). On August 29, 2014, jk-05 was approved by the General Logistics Department of Chinese People's Liberation Army for treatment of EVD in the army only for emergency. In the future, Sihuan Pharmaceutical (China) will invest 10 million RMB to collaborate with AMC for further development of this drug.

In September this year, a meeting consisting of Ebola scientists, industry executives, clinical-trials experts, ethicists, and regulatory officials was convened by WHO to identify and prioritize the most promising products for use in clinical trials against EVD. Besides ZMapp, TKM-Ebola, and jk-05, another four agents including two drugs (favipiravir and BCX4430) and two vaccines (cAd3-ZEBOV and VSV-EBOV) were considered as potential medications against EVD by the delegates (Table 1). Favipiravir, developed by Toyama Chemical of Japan, is an experimental anti-viral drug currently undergoing phase III clinical trials for influenza and was approved in Japan for stockpiling against influenza pandemics in 2014 (*10*). This drug was also demonstrated to be effective in a mouse model of EVD in preclinical studies. Favipiravir gave 100% protection against aerosol Ebola virus E718 infection in mice when administered at 1 h post-challenge and continuing twice daily for 14 days (*11*). In addition, initiation of favipiravir administration at day 6 post infection induced rapid Zaire Ebola virus clearance, reduced biochemical parameters of disease severity, and prevented a lethal outcome in 100% of the animals (*12*). These promising findings suggest favipiravir is a candidate for treatment of Ebola hemorrhagic fever. BCX4430, developed by BioCryst Pharmaceuticals (USA), shows broad-spectrum antiviral effectiveness against a range of RNA virus families including Ebola and Marburg viruses (*13*). BCX4430 has been demonstrated to protect against Ebola virus in rodent models (*13*). The development of this drug for use in humans is being fast-tracked. cAd3-ZEBOV and VSV-EBOV are experimental vaccines developed by GlaxoSmithKline (GSK, UK) and National Microbiology Laboratory (NML, Canada), respectively. cAd3-ZEBOV is derived from a chimpanzee adenovirus, Chimp Adenovirus type 3 (ChAd3), genetically engineered to express glycoproteins from the Zaire and Sudan species of Ebola virus to provoke an immune response against them (*14*). VSV-EBOV is based on the vesicular stomatitis virus, which has been genetically engineered to express Ebola glycoproteins so as to provoke an immune response against real Ebola virus (*15*). Phase I trials of these two vaccines were commenced in September and October 2014 (*16*). If this phase is completed successfully, the vaccines would be fast tracked for use in this Ebola outbreak.

Outbreaks of Ebola epidemics have occurred several times in parts of Africa since EVD was first identified in Zaire (now the Democratic Republic of Congo) in 1976. Not until this outbreak spread out of Africa did the international community realize the gravity and urgency against this epidemic. In the past several months, various aid including medical resources, armed forces, and donations from USA, European countries, China, *etc.* have arrived in African nations hardest hit by Ebola and played an important role in helping control the epidemic. The research and development of anti-Ebola drugs has correspondingly been speeded up in medically advanced countries. It is never too late to turn. Cooperation and collaboration across the world may be the best 'drug' in controlling epidemic diseases in this global village.

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