Development of vaccines based on replication-incompetent Ebola virus

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Ebola disease is a severe, often fatal disease caused by orthoebolaviruses, with a mortality rate of up to 90%. During the past decade, outbreaks of Ebola disease have occurred frequently in West African countries and the Democratic Republic of the Congo, resulting in many victims. In addition, in September 2022, an outbreak was caused in Uganda by Sudan virus, which is antigenically distinct from Ebola virus that caused the outbreaks in West Africa and the Congo. Two types of viral vector vaccines against Ebola disease have recently been approved, but concerns remain regarding their safety and manufacturing. Therefore, there is an urgent need to develop control measures to prevent or limit future Ebola outbreaks. Previously, we developed a replication-defective Ebola virus that lacks the coding region for the essential viral transcription activator VP30 (termed EbolaΔVP30) Halfmann et al., *PNAS*, 2008). EbolaΔVP30 replicates to high titers only in cell lines that stably express the VP30 protein. We demonstrated that inactivated Ebola ΔVP30 protects immunized non-human primates against lethal challenge with Ebola virus (Marzi et al., *Science*, 2015). We have since manufactured an inactivated EbolaΔVP30 virus vaccine (termed 'iEvac-Z') under GMP conditions and have conducted a Phase I trial at Research Hospital, the Institute of Medical Science, the University of Tokyo, which demonstrated that iEvac-Z induces virus-specific antibodies and has a strong safety profile in humans. For safety reasons, this Phase I study was conducted without an adjuvant. Accordingly, this research proposal aims to conduct a Phase I study of iEvac-Z with adjuvant to demonstrate safety and efficacy. Furthermore, we will develop a next-generation Ebola vaccine that can be used against orthoebolaviruses with different antigenic properties. The inactivated EbolaΔVP30 virus vaccine is expected to be safer and more effective than viral vector vaccines that express only GP because EbolaΔVP30 virus possesses other major viral proteins such as NP and VP40. Also, the use of the adjuvant is expected to induce neutralizing antibodies and cellular immunity. Ebola virus must be handled in a BSL-4 facility, whereas EbolaΔVP30 virus can be handled at a lower level of containment. This technology could, therefore, be applied to other BSL-4 viruses, such as Nipah virus, as a new vaccine modality and is expected to contribute greatly to vaccine development in Japan.