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A PLATFORM APPROACH FOR THE PRODUCTION OF HAND, FOOT, MOUTH DISEASE VACCINES

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Hand, Foot and Mouth Disease (HFMD) is an endemic childhood disease in Southeast Asia, with substantial disease burden affecting millions of children each year. Occasionally the central nervous system is involved causing serious and sometimes fatal neurological complications. HFMD outbreaks are also observed outside the Asia-Pacific countries. HFMD can be caused by multiple enteroviruses of which the best known virus is EVA71. However, also other enteroviruses such as CVA6, CVA10 and CVA16 can cause the disease. Inactivated EVA71 vaccines are registered in China, but in order to prevent all HFMD cases, multivalent vaccines are warranted. Intravacc is developing an HFMD combination vaccine.

Here we used our rescue platform to generate the starting materials required for vaccine production. Infectious clones from EVA71_B4, EVA71_C4, CVA6, CVA10 and CVA16 were constructed and the corresponding enteroviruses were rescued. Virus seeds were produced on Vero cells in animal component free medium. Rescued enteroviruses could efficiently replicate, resulting in seed lots with high viral titers. This rescue platform has the major advantage that clinical isolates are not required to obtain the starting material to produce a vaccine, thus mitigating the risk that other, unwanted, viruses are also present. Next to that, the virus source is pre-designed, controlled and well documented.

For a proof of principle study in mice, monovalent EVA71_C4 vaccine was prepared using our well-established enteroviral vaccine production platform. Vero cells were grown adherent to microcarriers in bioreactors (2.3L – 10L scale) in ACF media and infected at an MOI of 0.01. Virus was harvested when full cytopathic effects were observed. The enteroviruses were clarified, concentrated, purified and inactivated with formaldehyde. A first immunogenicity study with the inactivated EVA71_C4 vaccine in mice resulted in neutralizing antibody titers to EVA71_C4. These antibodies could also neutralize EV71_B4, but not CVA16, emphasizing the need of developing a multivalent HFMD vaccine.

After this successful proof of principle experiment, process development studies were started to draft a production process suitable for the production of multivalent HFMD vaccines that can be used for Phase I clinical trials.

Our viral vaccines platform forms a solid basis for rapid production of monovalent and multivalent HFMD vaccines by using molecular techniques to obtain different HFMD viruses and by using our enteroviral platform production process.