AN OUTBRED MOUSE MODEL OF YELLOW FEVER FOR STUDY OF PATHOGENESIS AND DEVELOPMENT OF VACCINES AND THERAPEUTICS

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Yellow fever (YF) is a mosquito-borne viral disease that is endemic in several African and South American countries. YF virus (YFV) causes subclinical infections with mild and non-specific symptoms, to severe, potentially lethal illness with jaundice, hemorrhage, and renal failure. Despite the existence of safe and efficient vaccines, epidemics continue to occur, mostly in Africa where the burden of YF is estimated to represent 1.7 million annual cases and up to 80,000 deaths per year. Moreover, emergence of YF has been reported in new, previously unaffected areas, because of the introduction of the mosquito vectors into these lands. There is no effective therapy against YFV infection but licensed vaccines are available, which are derivatives of a live attenuated strain that was first developed in 1937. These vaccines are currently being used in vaccination program in endemic countries and for travelers visiting these regions. They provide a long-lasting immunity against all the known genotypes of YFV. Although very rare, there are reports of serious adverse effects associated with these vaccines. One major drawback of YF vaccines is their preparation that is based on culture on embryonated eggs, a fastidious and lengthy process that limits the capacity to produce high volumes of stocks needed to respond to recurring epidemics and to prepare for a potential major outbreak. An effective therapy and new types of vaccine that can support rapid scale up is needed for efficient management of YF in the future. The best available animal models to enable these endeavors are currently non-human primates (NHP) in which YF cause a disease similar to human infection of YF. However, the cost of NHP studies is a limit to preclinical studies, in particular in the most affected areas of the globe. There are a few mouse models of YF. However, these models consist of genetically-deficient rodents that are not best suited to replicate the disease and to accurately evaluate new vaccines or therapies. We have developed a mouse model of YFV infection based on the Swiss Webster outbred strain. We have tested several epidemics isolates and identified strains that, when administrated by the intraperitoneal route, caused an acute infection leading to death. Interestingly, these YFV strains are lethal only when prepared from mouse organs and not when cultured on cell lines. We used this model to test the efficacy of the 17D YFV vaccine strain in protecting mice against lethal challenge showing that the model can be used to evaluate new YF vaccines and therapies.