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An outbreed mouse model of yellow fever for study of pathogenesis and development of vaccines and therapeutics

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An Outbreed Mouse Model of Yellow Fever Virus for Study of Pathogenesis and Development of Vaccines and Therapeutics

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BACKGROUND

Yellow fever (YF) is a mosquito-borne viral disease that is endemic in several countries of sub-Saharan Africa and South America. The World Health Organization estimates that YF causes 200,000 symptomatic cases and 30,000 deaths globally every year, with over 90% of reported cases and deaths occurring in Sub-Saharan Africa. However, other estimates propose much higher figures particularly in Africa. YF prevention is based on a vaccine that exist since 1937. This vaccine is derived from a live attenuated strain of YF virus that confers protection against the seven known YFV genotypes. An important limitation of the currently approved YF vaccines is their manufacture that is a fastidious and lengthy process that requires inoculation of embryonated eggs. This process has a limited capacity for rapid and high scale production to respond to massive outbreaks. Additionally, there are reports of the occurrence of fatal YF vaccine-associated disease which point to the need of new easily manufactured and highly scalable vaccines against YF. Animal models are important to vaccine development. Regarding YF, there are several animal models including mice, hamsters and non-human primates. The small animal models consist mostly of genetically-deficient inbreed mice that lack important functions of the immune system. In this work, we are developing a mouse model of YF using the outbreed Swiss Webster mouse strain.

METHODS AND RESULTS

We tested five YFV strains from the collection of the Institut Pasteur de Dakar (Table 1) for their ability to cause disease to Swiss mice after intraperitoneal administration. Virus stocks prepared from human or insect cell lines were well tolerated by the mice. In contrast, viruses collected from brain homogenates of newborn mice caused mortality to adult Swiss rodents after intraperitoneal administration (Table 2).

Table 1. Characteristics of Yellow Fever Virus strains tested in this study

STRAINS	YEAR	LOCATION	ORIGIN
YF-IPD1	1973	Ivory Coast	Mosquito
YF-IPD2	1995	Senegal	Mosquito
YF-IPD3	1995	Senegal	Mosquito
YF-IPD4	1995	Senegal	Mosquito
YF-IPD5	1991	Cameroon	Human

Table 2. Survival of Swiss mice infected with Yellow Fever viruses prepared from insect cell lines or from newborn brain homogenates

STRAINS	C6-36 (pfu)	BH-High (pfu)	BH-Low (pfu)
YF-IPD1	12/12 (5×10^5)	0/9 (5×10^7)	Fig. 1
YF-IPD2	12/12 (3×10^5)	6/12 (10^{10})	8/8 (5×10^2)
YF-IPD3	12/12 (10^5)	6/8 (10^{10})	5/8 (5×10^3)
YF-IPD4	12/12 (10^5)	6/6 (10^{10})	6/8 ($1{,}5 \times 10^3$)
YF-IPD5	12/12 (10^5)	6/6 (5×10^5)	4/8 (10^4)

The numbers in the table show the survivors over the total number of mice tested. C6-36, insect cell line; BH-High, high doses of virus from brain homogenates; BH-Low, low doses of virus from brain homogenates.

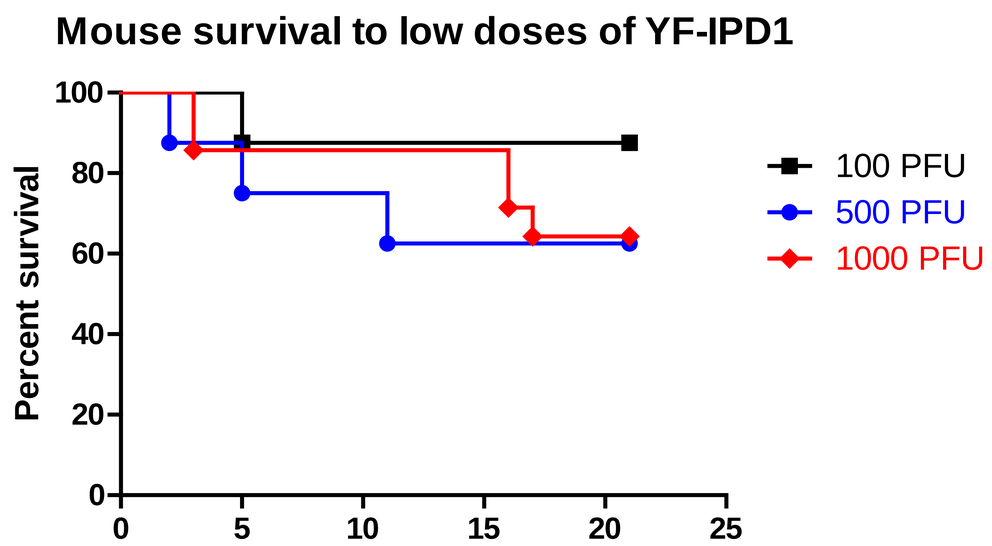

Figure 1. Strain YF-IPD1 from newborn brain homogenate is virulent at low doses in adult Swiss mice. Mice were infected by the intraperitoneal route with the indicated doses of virus and survival was followed for 21 days.

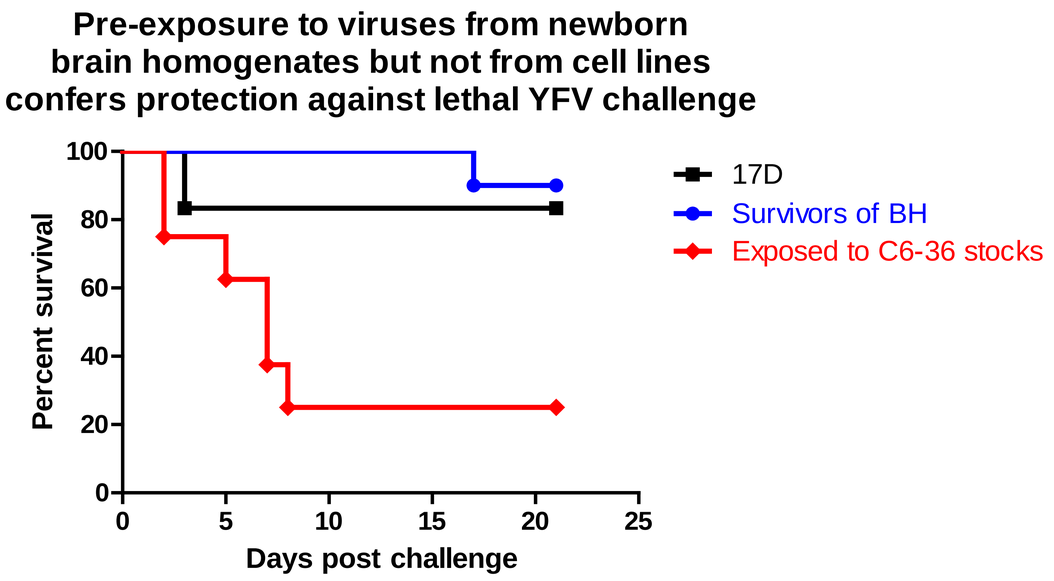

Figure 2. Pre-exposure to Yellow Fever viruses from brain homogenates but not from cell lines confer protection against lethal challenge with strain YF-IPD1. Mice immunized with the 17D Yellow Fever vaccine strain or survivors of the strains tested in this study were challenged one month later with a lethal dose of strain YF-IPD1 and the survival followed for 21 days.

Exposure to Yellow Fever Virus does not protect Swiss mice against other flaviviruses

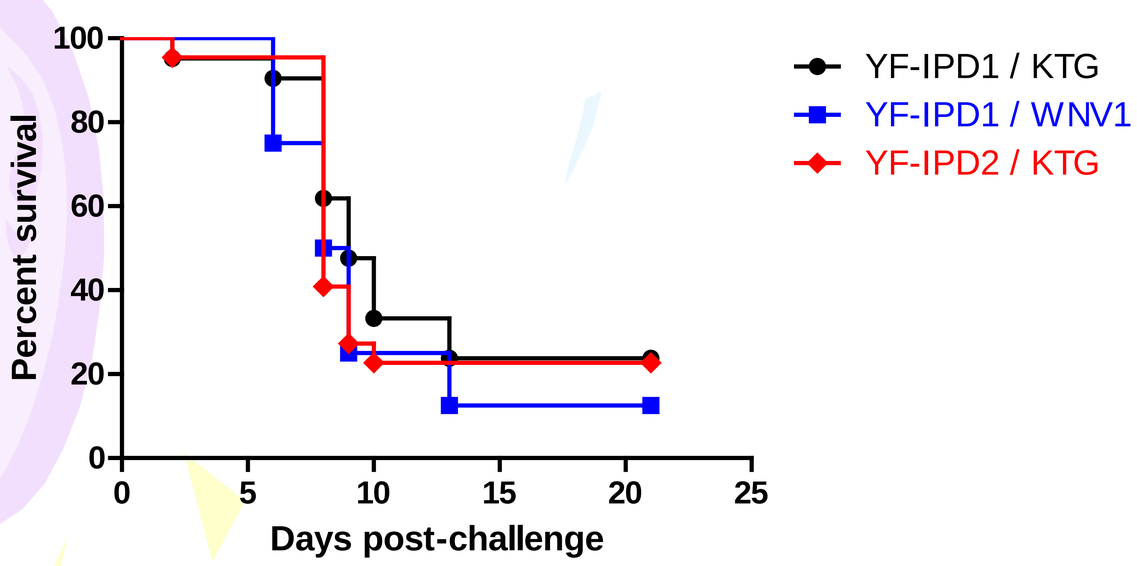

Figure 3. Exposure to Yellow Fever virus does not protect Swiss mice against West Nile Virus. Mice survivors of strains YF-IPD 1 and 2 were challenged 1 month after exposure with Lineages 1 (WNV1) or 7 (Koutango, KGT) of West Nile virus.

CONCLUSION

We showed that Yellow Fever virus prepared from brain homogenates of newborn mice can cause lethal disease to outbreed Swiss Webster mice. Prior exposure to non-lethal Yellow Fever virus confer protection against this challenge. This model could be used to study the pathogenesis of YF virus and to perform preclinical development of vaccines and therapeutics for YF.