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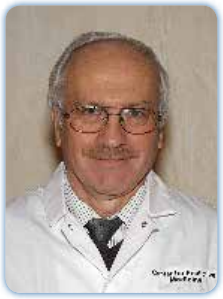

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Pan-Lassa fever vaccine for prevention and post-challenge applications

Lassa virus (LASV) has the highest human impact of any of the viral hemorrhagic fevers in Africa with an estimated several hundred thousand infections annually, resulting in thousands of deaths in West Africa. Currently, there is no licensed vaccine or FDA-approved treatment against Lassa fever (LF). Replication-competent attenuated vaccine represents the most feasible approach to control LASV. Arenaviruses have bi-segmented RNA genome and can produce reassortants after co-infection. We rationally selected the MOPV/LASV reassortants carrying the L segment encoding RNA polymerase from the non-pathogenic Mopeia virus (MOPV) and the S segment encoding major antigens (NP and GPC) from LASV/Jos. The final selected isolate, clone ML29, contained 18 mutations distinguishing ML29 from the parental viruses. These mutations additionally contributed to ML29 attenuation (Fig. 1). The ML29 was intensively tested in animal models including SIV-infected rhesus macaques mimicking HIV-infected individuals. The vaccine was well tolerated and efficacious. One single injection of 1,000 PFU of ML29 provided full protection against homologous challenge and protection against LF caused by LASV strains from distantly-related clades. ML29 was genetically stable during passages in vitro and in vivo. Recently, we have rescued recombinant ML29 (rML29) from cDNA clones and successfully applied tri-segment arenavirus technology. The goal of this approach is to develop rML29 as a vaccine platform. Replication of arenaviruses is accompanied by generation of defective interfering particles (DIPs). ML29 DIPs were generated in vitro during serial passages at high multiplicity of infection or in persistently infected cells. ML29-persistently-infected cells were resistant to LASV infection and this resistance correlated with the presence of DIPs. ML29 DIPs had large deletions (mostly in the L RNA). Guinea pigs fatally challenged with LASV and treated 2 days after challenge with ML29 DIPs were protected against fatal LF disease. These experiments demonstrate feasibility of ML29 DIPs design with potent therapeutic activities.

Biography

Igor S Lukashevich has a long-standing research interest in molecular biology, pathogenesis and prevention of diseases caused by Hemorrhagic Fever Viruses (HFVs). He has extensive experience with HFVs from his field work in West Africa and from his experimental work with Lassa, Machupo, Marburg, and Ebola viruses in high biocontainment facilities. He has more than 100 publications in this area. His recent research program has focused on Lassa fever pathogenesis and vaccine R&D. He designed and developed experimental reassortants ML29 and YF17D-based Lassa fever experimental vaccines. In collaboration with Dr. S Paessler (UTMB) and Dr. Juan C de la Torre (Scripps Res. Inst.), he is developing recombinant ML29 as a vaccine platform to control HFVs in African countries.

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