Title: Plasmid-based live-attenuated vaccines against yellow fever and other emerging infections

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Summary

For many infections, in particular several acute lethal viral infections such as yellow fever, Japanese encephalitis, rabies or Ebola for which no treatment exists, vaccination is the only means of prevention. Live-attenuated vaccines such as the yellow fever 17D (YF17D) legacy vaccine are among the most effective vaccines, due the high degree and longevity of protection they may provide; often from single-dose immunization. For instance, YF17D elicits immunity rapidly – usually within 7-10 days – that it may be used to curb outbreaks or for last-minute travel vaccination, for instance when personnel is dismissed to regions with a high risk of exposure. A major shortcoming inherent to almost all live vaccines is *(i)* their general sensitivity to elevated temperatures and *(ii)* complexity of manufacture. For instance, YF17D is still produced in embryonated chicken eggs as established more than 80 years ago, at a limited global production capacity and at risk of sever adverse effects (SAE; egg allergy/anaphylaxis; emergence and outgrowth of pathogenic variants in the final mixture of vaccine viruses). Taken together, these issues limit their wider use in the field.

Using the YF17D vaccine as viral vector and a convenient bacterial plasmid platform for manufacture, we developed PLLAV (Plasmid-Launched Live-Attenuated Vaccines) as a viable alternative to conventional live viral vaccines and explored their safety, immunogenicity and efficacy in stringent preclinical animal models, head-to head with licensed vaccines in current use. In contrast to conventional vaccines, PLLAV vaccines are genetically clonal and chemically defined as desirable for safety. Importantly, when YF17D is used as viral vector to produce novel transgenic vaccines against emerging encephalitic (Zika, rabies), hemorrhagic (Ebola) or respiratory viruses (COVID-19), the foreign antigen appears to consistently benefit from the strong immunogenicity of genuine YF17D, to trigger *(i)* a strong innate antiviral immunity, *(ii)* long-lasting antibody and *(iii)* polyfunctional cellular responses for vigorous protection. In addition, PLLAV-YF17D and derived vaccines benefit from the intrinsic stability of DNA and may therefore be stored and transported at elevated temperatures for several days, if not weeks. As such, PLLAV vaccines may become a viable alternative to existing vaccines for emerging infectious diseases This technology will be further developed and moved into clinical trials by the recently founded company AstriVax (www.astrivax.com).