

Live-Attenuated Tetravalent Dengue Vaccine Development at Mahidol University

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Dengue virus (DENV) is a mosquito-borne flavivirus endemic to tropical and subtropical regions of the world. Four antigenically related serotypes of DENV circulate in nature. While 2/3 of these infections are unapparent and non-symptomatic, clinical manifestations range from a self-limited febrile illness to a potentially fatal disease characterized by hemorrhage and/or shock.

As the immune response elicited by natural DENV infection confers life-long protection against re-infection by viruses of the same serotype, vaccination and immunologic protection against DENV should be feasible. The development of a DENV vaccine is complicated by a requirement to protect simultaneously against the four serotypes of DENV and the potential for a suboptimal vaccine-induced immune response to exacerbate disease.

The development of live attenuated tetravalent DENV vaccine has been actively pursued at Mahidol University since 1980 using a classical method of attenuation pioneered by Louis Pasteur, the serial passaging of a virulent organism in a non-natural host. The process selects for mutations that differ between viruses by selection mechanisms that are not well understood. Every method of producing a viral vaccine candidate results in a biological agent that must be thoroughly characterized and finally tested in human volunteers. Wild type DENV used for attenuation attempts at Mahidol had been derived from a population of viruses recovered from infected individuals which composed of viruses circulated as quasispecies populations of genetically different virions. The discovery of selection pressure on wild type DENV afforded by Primary Dog Kidney (PDK) cells was made. In this effort all 4 DENV replicated in PDK. Each of these viruses was tested individually at different passage levels for biological markers. Successful individual candidate vaccines were identified for all DENV1-4. When combined, the mixture of those viruses resulted in balance of immune responses among all the 4 serotypes in primates.

Extensive viral biomarker and clinical trial experience at Mahidol University revealed two conclusions concerning the use of PDK cells to select attenuated DENV vaccines: 1) serial passage in PDK cell uniformly selected for attenuation of all four DENV for human beings and 2) attenuation biomarkers appeared during each set of serial passages at approximately the same PDK passage level. This latter observation suggested that PDK passage subjected each of the four DENV with reproducible selective pressure.

As high potential vaccine candidates, such a live attenuated tetravalent DENV vaccine was licensed to vaccine biopharmaceutical industry for production scale up. After decades of working with live attenuated dengue vaccines, several objectives could be achieved. The safe and well tolerated vaccines could be identified. Strong and long lasting immune responses could be obtained as a result of using suitable virions similar to natural viruses which still could elicit strong stimulation to both the humoral and cell mediated immunities. The prospects for these DENV vaccine innovations are very promising.