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Dengue fever (DF) and its more severe manifestations, namely, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), are caused by infection with the mosquito-borne dengue viruses, which are members of family Flaviviridae. There are four closely related, antigenically distinct, serotypes (1-4) of dengue viruses, each of which can cause a severe disease. In recent decades, there has been a dramatic increase in the incidence of dengue infections, with about 100 million cases of DF occurring each year. There is no licensed vaccine available to immunize the 2.5 billion people living in dengue endemic regions of the world. The challenge is to develop a dengue vaccine, which is safe, efficacious (against all four DEN serotypes) and inexpensive. The live flavivirus-based vaccine strategies currently being pursued, suffer from key drawbacks. Genetic instability (and the resultant potential to revert to virulence), viral interference (and the associated imbalance in immune response with the inherent risk of ADE), the possibility of secondary transmission by mosquitoes and the potentially high cost factor will together make it very difficult, in fact almost impossible, to address this challenge.

We propose to create a novel recombinant ‘tetravalent’ dengue vaccine based on host cell receptor binding domains III of the E proteins of all four DEN viruses. We plan to express recombinant domain III of the four DEN serotypes as a fusion protein, in which domain III from all four serotypes are joined in a ‘beads-on-a-string’ fashion (tetravalent antigen), in the methylotrophic yeast *Pichia pastoris*. The choice of domain III as a vaccine candidate and the choice of *Pichia pastoris* as an expression host have three important outcomes from the perspective of developing a dengue vaccine. Firstly, domain III lacks cross-reactive epitopes that can evoke enhancing antibodies. Secondly, it carries only neutralizing epitopes that can elicit protective immunity. Finally, the *P. pastoris*-based expression system is associated with high productivity of functional recombinant proteins. Thus, this scheme has the potential to pave the way towards developing a safe, efficacious and inexpensive ‘tetravalent’ dengue vaccine for use in countries where it is needed the most.