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Dengue is a mosquito-borne viral disease caused by four closely related, yet antigenically distinct, RNA viruses (serotypes 1-4) of the *Flaviviridae* family. Infection with dengue viruses has emerged as a leading global public health concern. No vaccine is currently licensed for human use. Developing a dengue vaccine has been an elusive goal for several reasons. One of the major hurdles is the existence of a phenomenon known as antibody dependent enhancement (ADE), wherein cross-reactive antibodies from a prior infection can contribute to potentially fatal disease during infection with a different serotype. Consequently, a successful dengue vaccine is expected to be 'tetravalent', that is, provide solid and long-lasting immunity to each of the four dengue virus serotypes.

The major focus of current dengue vaccine development efforts is on the use of live-attenuated and infectious clone-derived vaccines. Currently, six different virus-based vaccines are in advanced stages of development. Two of these are traditional tissue culture based live attenuated vaccines whereas the remaining four are chimeric recombinant vaccine viruses developed using infectious clone technology. In all these instances, the vaccine viruses are 'monovalent' in that each one is specific to one dengue serotype. A 'tetravalent' dengue vaccine is produced by mixing the four monovalent vaccines. Recent studies have shown that such tetravalent dengue vaccine formulations elicit unbalanced immune response due to viral interference. Obviously, this is associated with the risk of ADE-mediated fatal disease.

The work presented in this thesis contributes to a paradigm shift in the approach to dengue vaccine development. Moving away from a 'four component' tetravalent attenuated RNA virus-based vaccine, it examines the possibility of switching to a DNA-based 'single' tetravalent vaccine carrier, as an approach to circumventing the problem of viral interference. Two factors, namely (i) promising progress in the development of adenovirus as a vaccine vector platform and (ii) the emergence of dengue virus envelope domain III as a unique serotype-specific antigenic region with excellent sub-unit vaccine potential, in recent years, have provided the foundation for this work.