Chapter 2

Aims and Objectives
2. Aims and objectives

Dengue is a mosquito borne viral disease, which has emerged as a major global public health problem of the current century. Each of the DEN serotypes is capable of causing disease. Sequential infection in areas of hyperendemicity with different serotypes can precipitate fatal consequences through the mechanism of ADE. As a result, it is widely accepted that a safe dengue vaccine must be tetravalent, capable of conferring solid and long lasting protection towards all four DEN serotypes. This is one of the major hurdles that have made DEN vaccine development a challenging task.

Current DEN vaccine efforts, which focus on ‘monovalent’ live attenuated vaccine viruses of all serotypes, rely on mixing these together to generate tetravalent formulations. A major concern with such a strategy is the phenomenon of ‘viral interference’ resulting in immune responses to one serotype dominating the others. This is believed to stem from the acquisition of enhanced replication potential by the attenuated RNA genomes of one of the vaccine viruses in the tetravalent formulation. This unbalanced immune response, instead of imparting protection, can present a very risky situation of vaccine induced ADE phenomenon.

This work is based on the premise that switching to a DNA based vector system (such as that afforded by Ad vectors) to develop a single vaccine vector encoding critical antigenic determinants unique to each DEN serotype (such as the DEN EDIIIs) may help circumvent viral interference. Thus, the main objective of this study is to create recombinant Ad vectors expressing chimeric DEN EDIII-based multivalent molecules and to evaluate their capacity to elicit immune responses towards the cognate DEN serotypes. The specific aims are:

- Isolation of cDNAs encoding EDIIIs of single DEN virus serotypes (monovalent genes).
- Construction of a rAd vector expressing EDIII of a single serotype (monovalent rAd).
- Investigation of the potential of the monovalent rAd to serve as a DEN vaccine carrier.
Aims and objectives

- The design of a ‘bivalent’ EDIII chimeric construct by linking EDIIIs of two DEN virus serotypes.
- Preliminary evaluation of the ‘bivalent’ antigen’s ability to manifest antigenic attributes of its monovalent precursors.
- Transfer of the bivalent construct into a rAd vector, evaluation of the capacity of the resultant bivalent rAd to elicit immune responses to two DEN virus serotypes.
- Assembly of a ‘tetravalent’ EDIII-based gene and the generation of the corresponding tetravalent rAd vector.
- Analysis of the capacity of the tetravalent rAd vector to elicit immune responses specific to each one of the four DEN virus serotypes.