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Live attenuated tetravalent dengue virus host range vaccine elicits immune response in African green monkeys

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Abstract

Dengue fever is becoming increasingly common in tropical and subtropical regions throughout the world and recent outbreaks in the continental USA highlight the widespread threat to public health. Dengue virus (DV) is transmitted by mosquitoes and as distribution of these insects has expanded, so have cases of dengue fever. DV is a member of the Flavivirus family and has 4 distinct serotypes (DV1, 2, 3 and 4). No cross protection is afforded to a heterologous serotypes following infection by any one of the individual serotypes. In addition, the presence of antibodies to one serotype of DV can facilitate the occurrence of the more severe dengue hemorrhagic fever through immune enhancement upon infection with a second serotype. For this reason, the development of a safe, tetravalent vaccine to produce a balanced immune response to all four serotypes is absolutely critical. Arbovax employs a novel dual-function platform technology to develop safe and effective live-attenuated vaccines coupled with a low cost system of manufacture to target DV and other insect-borne viruses. Host range (HR) mutants of each DV serotype were created by truncating the transmembrane domain of the E protein and selecting for strains of DV that replicated well in insect but not mammalian cells. Four experimental groups (n=4 animals per group) of African green monkeys were vaccinated with a tetravalent DV HR vaccine in four separate injections, one into each limb. Each group was challenged with one serotype of wild type DV. Four negative control groups (n=4 animals/group) were injected with diluents only and each group was similarly challenged with only one serotype of wild type virus (DV1-4). No vaccine related adverse events occurred. The vaccine strains were confirmed to be attenuated in vivo by infectious center assays. Appropriate IgG responses to each DV serotype were also detected by ELISA. $PRNT_{50}$ revealed that all animals seroconverted 100% to DV1, 2, 3 and 4. The DV HR tetravalent vaccine was also able to protect animals from challenge with a virulent DV strain. Post-challenge viremia was decreased by a factor of 10 as compared to unvaccinated animals. These DV HR mutants are good candidate vaccines that can go on to human trials. Overall, this method for the creation of live, attenuated viral vaccines that generate safe and effective immunity may be applied to many other insect-borne viral diseases for which no current effective therapies exist.

Biography

Malcolm Thomas is president and CEO of Arbovax, a biotechnology company commercializing a unique and innovative platform technology that can be used to make vaccines against insect-borne viral diseases. The company is currently working on Dengue Fever and Chikungunya vaccines. Prior to Arbovax he was Vice President of Operations for StemCo Biomedical and before that, was Director of International Marketing for Bayer Biologicals and Vice President of Pacific Rim Operations for Becton Dickinson Biosciences. During his tenure with Becton Dickinson as Vice President for Asia Pacific he lived in Singapore for 5 years. He started his working life as a research scientist in the biochemistry department of the Wellcome Research Laboratories in the UK.