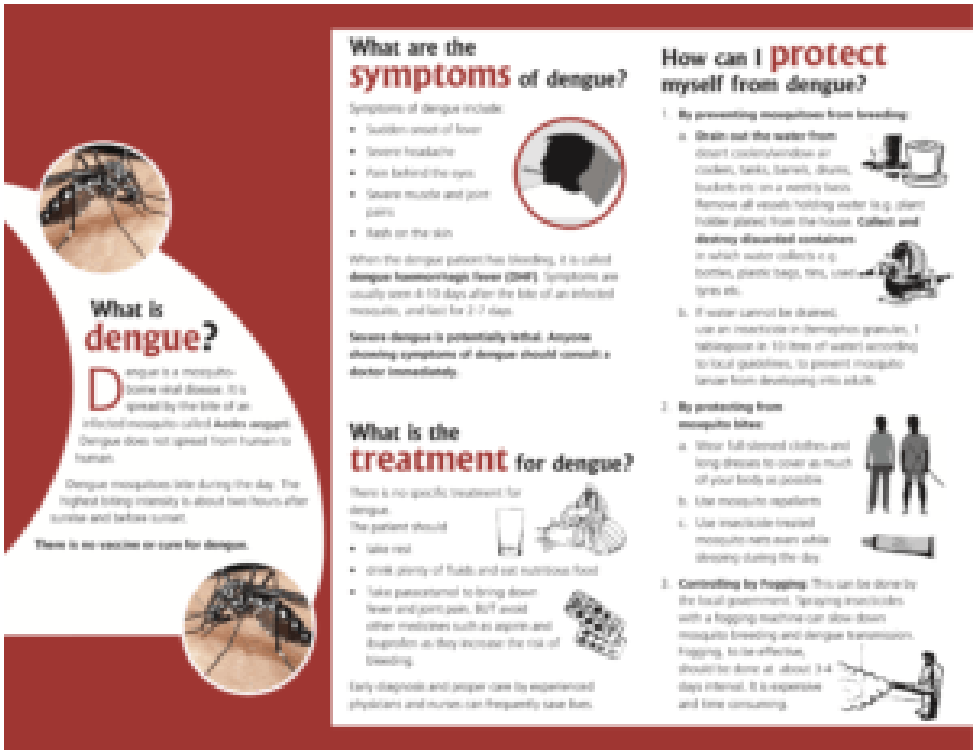
TAK-003 induces functional DENV cross-reactive cellular immmunity



Dengue Infographic Source: http://www.searo.who.int/entity/vector_borne_tropical_diseases/topics/dengue/Dengue.pdf?ua=1

Dengue virus (DENV) transmitted by *Aedes aegypti* causes dengue fever (DF), dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS). DENV infection induces lifelong which is specific for the infecting serotype, and subsequent infection with a different serotype often leads to severe DHF/DSS. This

severity has been suggestively attributed to antibody-dependent enhancement or T cell original sin. As a result development of DENV vaccines would have to induce immunity to all serotypes.

Dengvaxia® (CYD-TDV) developed by Sanofi-Pasteur, is a live-attenuated vaccine containing a virus backbone that expresses envelope protein (Env) from DENV1-4. The WHO Global Advisory Committee on Vaccine Safety, recommends the use of Dengvaxia® in areas of high DENV endemicity to reduce the increased risk of DHF/DSS in individuals naïve to wild DENV infection. Takeda Pharmaceutical Company Limited has also developed a DENV vaccine -TAK-003- which recently achieved its phase 3 efficacy end point. TAK-003 is a live attenuated vaccine that expresses precursor membrane (prM) and Env from DENV1-4.

A study by Waickman *et al.*, aimed to investigate T cell responses induced by TAK-003. They showed that TAK-003 induces strong CD8 T cells (IFN-γ+CD107+) responses that last for at least 120 days. Induced cellular immunity was reactive to the entire DENV proteome and cross-reactive to all 4 serotypes. Metabolic profiling of T cells in TAK-003 vaccinees showed that CD8 T cells that had high functional and proliferative activity expressed high levels of transferrin receptor (TfR1). Upregulation of TfR1 was observed in both vaccine-specific and non-specific CD8 T cells. These results implicate the iron pathway in vaccine-induced immunity and suggest that manipulation of this pathway following vaccination could improve vaccine-induced immunity.

Journal Article: Waickman *et al.*, 2019. Dissecting the heterogeneity of DENV vaccine-elicited cellular immunity using single-cell RNA sequencing and metabolic profiling. Nature Communications