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ANTIVIRAL DRUGS

# Novel antibodies defeat dengue virus

The mosquito-borne dengue virus (DENV) is a major human pathogen that can lead to potentially fatal dengue haemorrhagic fever. There are currently no specific treatments or vaccines available. Now, two papers report the therapeutic efficacy of monoclonal antibodies (mAbs) directed against novel epitopes within the viral envelope protein in mouse models of severe DENV infection.

DENV may be caused by any of four DENV serotypes, DENV-1–DENV-4. Antibodies generated against one serotype do not protect against other serotypes, but rather enhance subsequent infection. This phenomenon — known as antibody-dependent enhancement (ADE) of infection — occurs owing to viral particles binding to existing antibodies, enabling interaction with monocytic Fc receptors, which increases virus infection. A safe DENV vaccine must therefore potently neutralize all four serotypes. Although a tetravalent vaccine candidate is currently in clinical development, it has so far demonstrated only limited efficacy, especially against DENV-2.

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Fibriansah *et al.* therefore focused their studies on the DENV-2 serotype. They utilized DENV-2-specific human mAb 2D22 (hmAb 2D22), which has been previously shown to exhibit potent neutralization capacity. In mice, they demonstrated that hmAb 2D22 protected against DENV-2 when administered 24 hours before or 24 hours after DENV-2 inoculation.

More importantly, in mice pretreated with a lethal infection-enhancing dose of anti-DENV-1 serum, administration of a mutant hmAb 2D22 variant (exhibiting mutations in L234A and L235A in the full-length heavy chain) that was unable to bind to Fc receptors, 24 hours before inoculation with DENV-2, prevented ADE and the development of lethal vascular leak syndrome.

Next, the authors set out to understand the molecular features of the hmAb 2D22-targeted epitope. DENV-neutralizing antibodies typically target the viral envelope proteins (E proteins), which comprise 3 domains, DI–DIII, and exist as dimers. Cryo-electron microscopy-enabled determination of the structures of hmAb 2D22 complexed with each of two different DENV-2 strains revealed that the hmAb bound across dimeric E proteins, locking both ends of the dimers — thereby preventing the E protein reorganization that is required for virus fusion.

Meanwhile, Robinson *et al.* set out to develop a novel antibody directed against the E protein DIII (EDIII). Although EDIII-specific antibodies are probably only a minor component of the human humoral response, they exhibit high potency. First, using structure-based connectivity network analysis, the authors characterized the epitope–paratope interface on EDIII of a previously identified EDIII-directed antibody, 4E5A. This enabled prediction of a complementarity-determining region (CDR)-proximal deletion that enhanced epitope–paratope complementarity, resulting in the optimized antibody candidate, Ab513.

*In vitro*, Ab513 bound with high affinity to a diverse set of EDIII proteins, potently neutralizing various challenge DENV-1–DENV-4 strains, with similar or better potency than did a range of previously identified DENV-neutralizing antibodies. Notably, further investigation revealed that Ab513 neutralization of DENV could occur despite monocytic Fc receptor-mediated uptake.

In mice infected with DENV-2, a single prophylactic dose of Ab513 neutralized the virus, preventing viral migration to the central nervous system. Moreover, a single dose of Ab513 administered before or after infection prevented thrombocytopenia in a humanized mouse DENV model across all four DENV serotypes. Importantly, in a maternal-transfer model of lethal ADE (in which mice born to mothers that are immune to DENV-1 were infected with DENV-2), Ab513 treatment given 1 day post-infection efficiently prevented disease enhancement, whereas all control ADE mice died from the DENV-2 infection.

The ability of hmAb 2D22 and Ab513 to prevent ADE, in conjunction with the molecular understanding of their epitopes, provides new directions for the development of novel DENV vaccines and therapeutics.

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**ORIGINAL RESEARCH PAPERS** Fibriansah, G. *et al.* Cryo-EM structure of an antibody that neutralizes dengue virus type 2 by locking E protein dimers. *Science* **349**, 88–91 (2015) | Robinson, L. N. *et al.* Structure-guided design of an anti-dengue antibody directed to a non-immunodominant epitope. *Cell* **162**, 493–504 (2015)