

A New Infection Model Incorporates Genetic Diversity

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West Nile virus (WNV) is a member of the Flaviviridae family and is transmitted to humans by mosquito bites. So far, no vaccine or treatment is available and the only prophylactic strategies consist of preventing mosquito bites by using insect repellents or wearing protective clothing. The outcome of the infection is variable: while most people do not manifest any symptoms, about 1 in 5 develop a fever and of these, 1% has a severe, sometimes fatal, neurologic illness characterized by encephalitis, meningitis and acute flaccid paralysis.

Limited knowledge is available on the immune response to WNV in humans due to the high prevalence of non-symptomatic cases. Although several studies have been performed on inbred B6 mice, the infection in this model is less informative because it lacks the genetic diversity observed in humans.

A collaborative effort between Fred Hutch, University of Washington, University of North Carolina at Chapel Hill and Emory University led to the generation of a new model to study the immune response to WNV infection, the Collaborative Cross (CC) mouse. The CC model was obtained by crossing eight different mouse strains, including 5 classical inbred strains and 3 wild type derived strains. Recombinant inbred strains were generated by three generations of funnel breeding followed by at least 20 generations of inbred mating to develop each line.

Researchers Jessica Graham and Jessica Swarts from Jennifer Lund's Laboratory (Vaccine and Infectious Disease Division), together with their collaborators, investigated the effects of WNV infection on different CC strains and reported their results last month on the journal *mBio*.

Their results showed that the model was closer to ideal based on its ability to recapitulate the variability of the human disease outcome. First, three different disease phenotypes were observed: asymptomatic, symptomatic and asymptomatic with central nervous system (CNS) involvement. Asymptomatic mice did not show clinical signs, the ones with CNS involvement had inflammatory infiltrates in the brain, and symptomatic mice showed severe clinical scores and weight loss starting at day 7 after infection. Early innate immune responses, estimated by the expression of interferon beta and IFIT1, a molecule modulated by type I interferons, were associated with a better outcome.

In fact, while in asymptomatic mice the two genes were up-regulated at early time points and then decreased, in symptomatic mice they remained elevated at later time points as a possible consequence of the lack of viral control. A more complex situation was observed in the adaptive immune responses. While WNV-specific IgM and T cells increased at early time points to then decrease after the infection was cleared from the periphery in asymptomatic mice, the symptomatic strains showed diverse responses.

Finally, the researchers addressed the genetic variability of the CC mice by evaluating the relationship between two different allele classes and disease outcome for the gene *Oas1b*, encoding a protein with known antiviral function. The researchers showed that strains homozygous for the classical inbred allele had an enhanced propensity for a symptomatic disease outcome, while the wild-type allele was correlated with a symptomatic disease outcome.

"The CC model allows us to link rare outcomes with host genotype to identify genes of susceptibility and protection from WNV infection and disease," explains Dr. Graham. "This can assist us in identifying unique correlates of protection from neuroinvasive viral infections to inform therapeutic and vaccine strategies for controlling WNV infection in humans." In sum, the new CC mouse model better recapitulate the variety of WNV infection outcomes observed in humans: do we have a new, better model for infectious disease research?

[Graham JB, Thomas S, Swarts J, McMillan AA, Ferris MT, Suthar MS, Treuting PM, Ireton R, Gale MJ, Lund JM](#). 2015. Genetic diversity in the collaborative cross model recapitulates human west Nile virus disease outcomes. *MBio* 6(3):e00493-15.

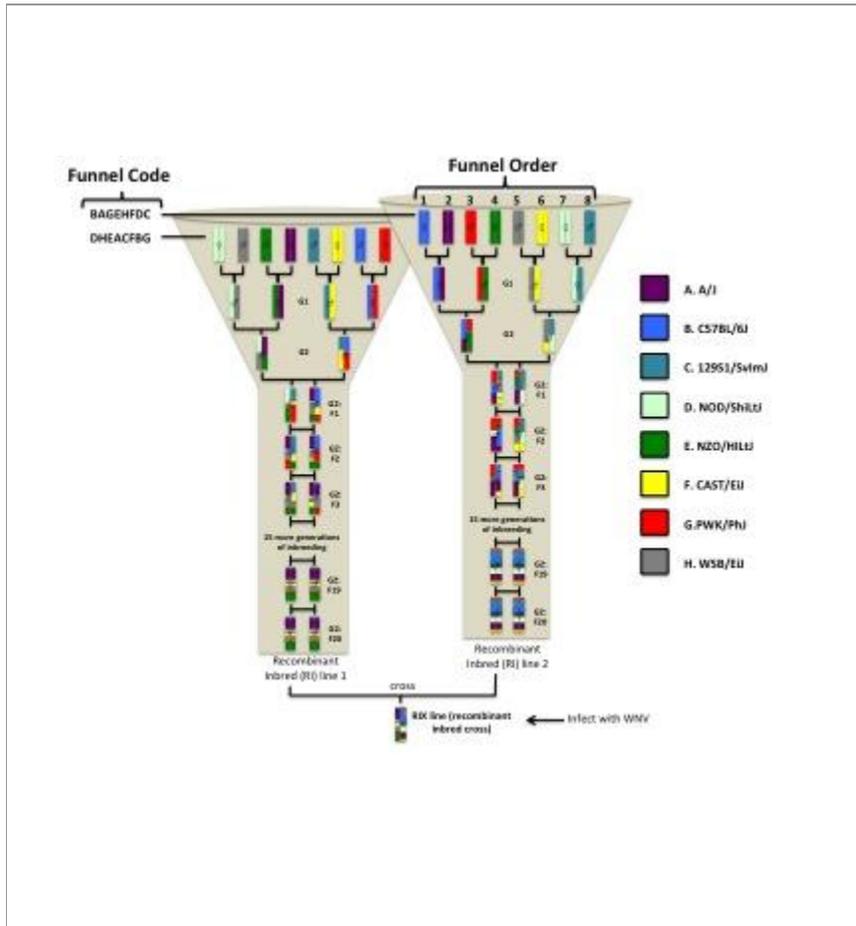


Image provided by Ms. Jessica Swarts

Schematics representing the generation of the genetic diversity in the CC mouse model.