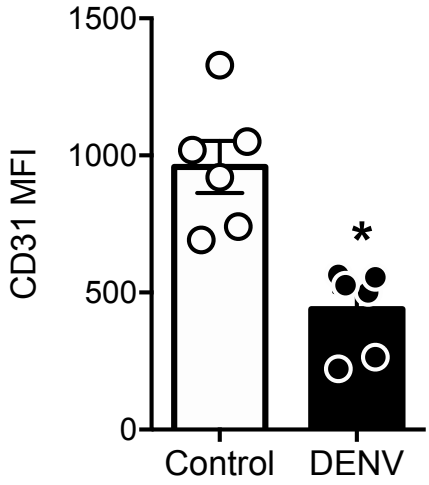
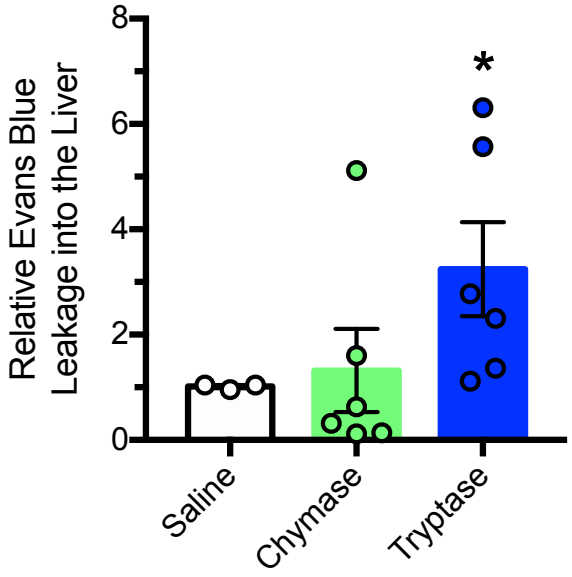
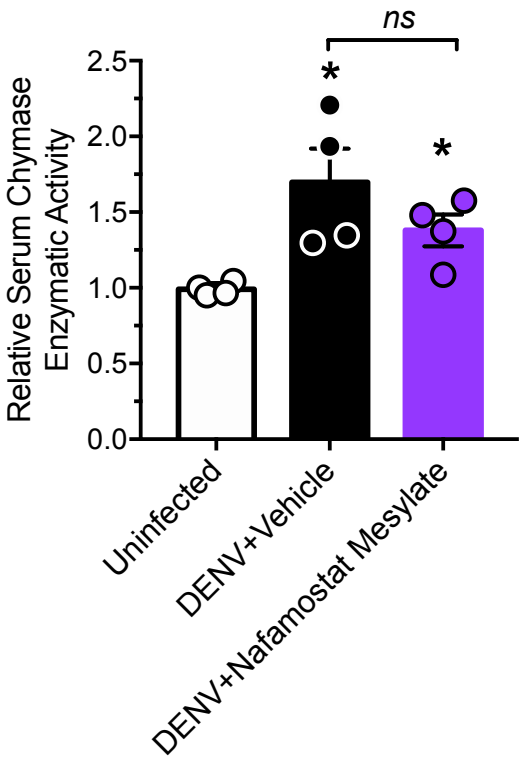
Supplementary Figures:



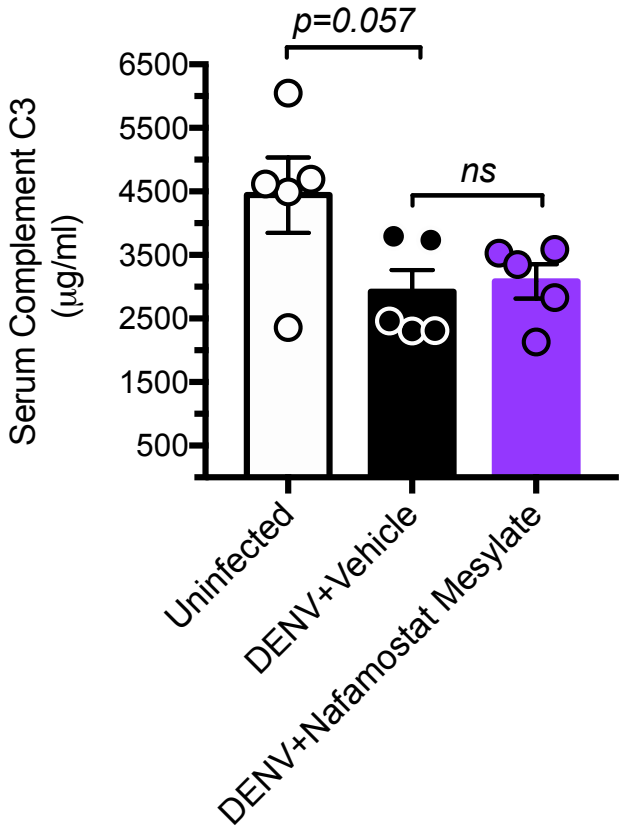
Supplemental Figure 1: Dengue infection reduces expression of adhesion molecule CD31 on vascular endothelium. Mean fluorescence intensity (MFI) of CD31 expression on endothelial cells determined by flow cytometry of cells isolated from mouse (n=6) footpads 24h after injection with $1X10^5$ PFU of DENV or saline control. $p<0.05$ by Student's un-paired t-test and error bars represent the SEM.



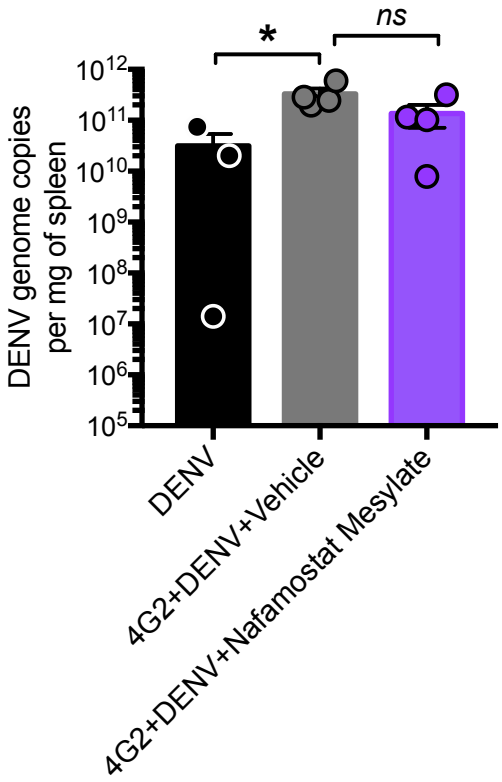
Supplemental Figure 2: Exogenous tryptase induces vascular leakage in mice. Evans blue dye leakage values were obtained in vivo in the liver of WT mice, 6h after i.v. injection with saline alone or 30ng of either tryptase or chymase. For the saline control group, n=3, for tryptase n=6 and for chymase n=6 animals were used. Tryptase treatment significantly enhanced Evans blue dye leakage (vascular leakage) in mice. $P<0.05$ determined by 1-way ANOVA using Holm-Sidak's multiple comparison test and error bars represent the SEM. Vascular leakage was assessed using a previously described method(1).



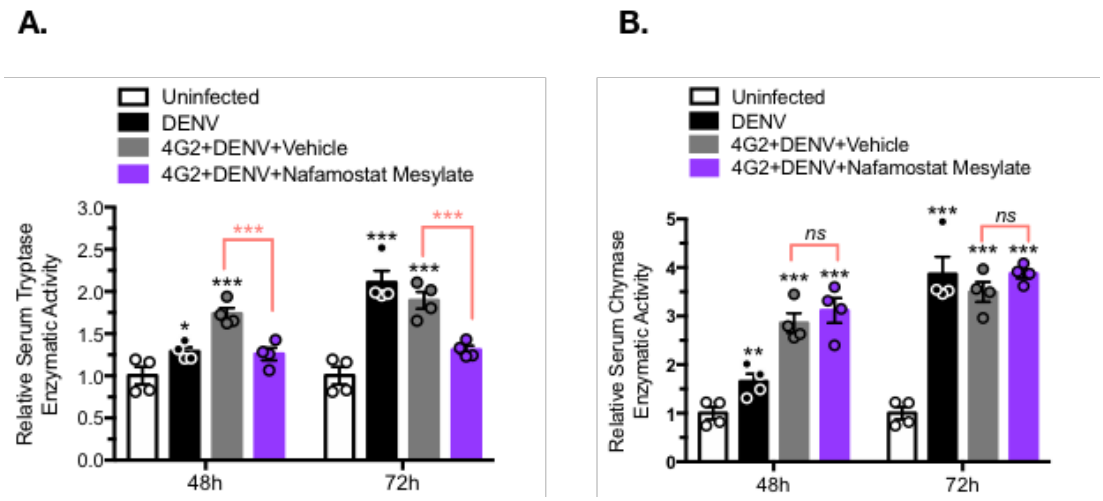
Supplemental Figure 3: Chymase activity was unaltered by treatment with tryptase inhibitor, nafamostat mesylate. WT mice (n=4 per group) were either mock-infected (uninfected) or infected with DENV ($1x10^6$ PFU) followed by treatment with vehicle control (saline) or using a specific tryptase inhibitor, nafamostat mesylate. At 24h, serum was isolated to measure chymase activity by enzymatic assay. Chymase activity was significantly increased up on DENV infection, however nafamostat mesylate treatment had no effect on chymase activity, suggesting the specific action of nafamostat mesylate on tryptase in vivo. Significance was calculated using Student's unpaired t-test and considered significant when $p<0.05$. Error bars represent the SEM.



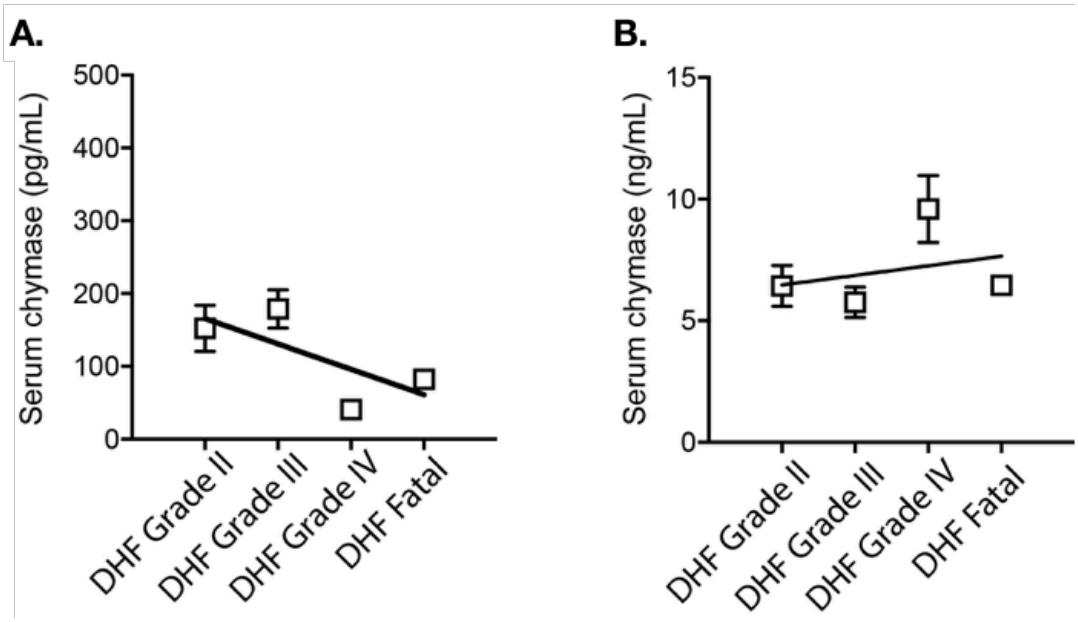
Supplemental Figure 4: DENV infection lowers the concentration of complement C3 in vivo, which is unaffected upon treatment with nafamostat mesylate. WT mice (n=5 per group) were infected with DENV ($1x10^6$ PFU) and either mock treated or treated with nafamostat mesylate. At 24h, serum was collected to measure the amount of complement C3 by ELISA. DENV infection lowered the amount of C3 protein in the serum, suggesting complement activation, which was approaching statistical significance by Student's unpaired t-test (p=0.057) or 1-way ANOVA (p=0.0512). Nafamostat mesylate treatment had no significant effect on the concentration of complement C3 during DENV. Error bars represent the SEM.



Supplemental Figure 5: Antibody dependent enhancement of DENV infection in AG129 mice. AG129 mice (n=3-4 per group) were passively given 50μg/mouse of an antibody 4G2, followed by infection with a high dose ($1x10^8$ PFU) of DENV i.p after 24h. For the treatment group, mice were treated with 0.6 mg/kg of nafamostat mesylate. At 24h, spleens were harvested for quantification of viral genome copies using quantitative real time RT-PCR. DENV infection was significantly enhanced in the presence of antibody 4G2; *$p<0.05$, calculated using Student's unpaired t-test. Nafamostat mesylate treatment had no effect on the viral load in mice. Error bars represent the SEM.



Supplemental Figure 6: Nafamostat mesylate treatment inhibits tryptase activity but not chymase activity in vivo in an antibody-enhanced DENV infection model. Severe DENV infection was induced in AG129 mice (n=4 per group) by passively giving them antibody 4G2, followed by infection with DENV. Mice were treated with 0.6 mg/kg of nafamostat mesylate or vehicle at 24h intervals. Days 2 and 3 post-infection, both serum (**A**) tryptase and (**B**) chymase activities were significantly enhanced during DENV infection. Nafamostat mesylate treatment significantly reduced DENV induced (**A**) tryptase activity but had no significant effect on (**B**) chymase activity. Statistics were calculated using 2-way ANOVA with Tukey's multiple comparison test and Student's unpaired t-test and significance is indicated as *** for $p<0.001$, ** for $p<0.01$ and * for $p<0.05$. Error bars represent the SEM.



Supplemental Figure 7: Serum chymase levels were not strongly correlated with the grade of DHF. Serum chymase levels were not correlated with the grade of DHF for patients in the (**A**) Indonesian cohort ($p=0.29$, $R^2=0.5$) or (**B**) Sri Lankan cohort ($p=0.71$, $R^2=0.09$). Error bars represent the SEM.

1. St John AL, Rathore, A. P. S., Raghavan, B., Ng, M. L., Abraham, S. N. Contributions of mast cells and vasoactive products, leukotrienes and chymase, to dengue virus-induced vascular leakage. *eLife.* 2013.