Discovery of Dengue Virus NS4B Inhibitors

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Background/Objective
Dengue virus serotype DENV-1 to -4 represent the most prevalent mosquito-borne viral pathogen in humans. No clinically approved vaccine or antiviral is currently available for DENV.

Method
We employed a series of cell base assays, mutation analysis studies, genetic studies, immunofluorescence assay (IFA) and in vivo study in this study.

Result
The inhibitor was identified through DENV-2 replicon assay using a high through put screening of 1.8-million compound library. The compound selectively inhibits DENV-2 and -3 (EC5010-80 nM), but not DENV-1 and -4 (EC50 >20 μM). Resistance analysis showed that a mutation at amino acid 63 of DENV-2 NS4B (a non-enzymatic transmembrane protein and a component of viral replication complex) could confer resistance to compound inhibition. Genetic studies demonstrate that variations at amino acid 63 of viral NS4B are responsible for the selective inhibition of DENV-2 and -3. Medicinal chemistry improved the physicochemical properties of the initial "hit" (compound-1), leading to compound-14a that has good in vivo pharmacokinetics. Treatment of DENV-2-infected AG129 mice with compound-14a suppressed viremia, even when the treatment started after viral infection.

Conclusion
These results have proved the concept that inhibitors of NS4B could be a potential target for clinical treatment of DENV infection. Compound-14a represents a potential preclinical candidate for treatment of DENV-2 and -3 infected patients.