Contribution ID: **131** Type: **Poster Presentation**

Ranking dose-normalized antiviral effect of drug combination treatments against hepatitis C virus

Monday, 9 July 2018 19:45 (15 minutes)

Since many kinds of Direct Acting Antivirals (DAA) have become the main treatment instead of interferon-α (IFN-α) against hepatitis C virus (HCV), combinations of these DAA are now standard treatment strategies. These treatments are very effective, however, at the same time, this provokes the problems which drug combination is more or most effective for each patient. Therefore, we established a viral replicon system for HCV to quantify the efficacy of each drug or drug combination easily. In this study, we used 15 different kinds of DAA (telaprevir, danoprevir, asunaprevir, simeprevir, sofosbuvir, VX-222, dasabuvir, nesbuvir, tegobuvir, daclatasvir, ledipasvir, IFN-α, IFN-λ, cyclosporin A, and SCY-635) and quantified the efficacy of (single and) multiple drug combinations using the replicon system. Then, we calculated instantaneous inhibitory potential (IIP) which captures the effectiveness of each drug combination as a function of the drug concentration. Furthermore, we defined and calculated the critical concentration index (RCI) that achieves 95% reduction in HCV replication is shown for each drug combination. The RCI intrinsically varies among the drug combinations. As an example, we found SMV&IFN-α yielded the lowest RCI values among the tested double-combinations. We would like to further discuss how our framework could enable drug usage optimization by quantifying the antiviral activity in preclinical settings, and presenting basic evidences for cost-effective drug selection.

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Session Classification: Poster Session

Track Classification: Disease - infectious