ined. We quantified those transcripts in paired tumor and non-tumor tissues from 18 patients. MYBL2, CDC2, and CCNA2 were significantly over-expressed in 15, 17, and 17 tumors, respectively, compared with their non-tumorous counterparts. There were significant correlations between expression levels of MYBL2 and CDC2, or CCNA2. SiRNA-mediated knockdown of MYBL2 reduced expression of CDC2 and CCNA2, and inhibited the growth of HCC cells. Conclusions: MYBL2, CDC2, and CCNA2 were frequently up-regulated in HCC. E2Fs control transcription of both G1/S-regulated genes (including MYBL2) and G2/M-regulated genes (including CDC2 and CCNA2). Our results were compatible with the recent finding that E2Fs, together with B-Myb, transactivate CDC2 and CCNA2, and therefore link the regulation of genes at G1/S and G2/M (EMBO J 2004;23;4615-26). B-Myb may promote the growth of HCC cells, in part through activation of CDC2 and CCNA2.

Disclosures:
The following people have nothing to disclose: Tomoaki Nakajima, Kohichiroh Yasui, Yoshito Itoh, Shigeki Arii, Johji Inazawa, Takeshi Okanoue

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AN EFFICIENT CELL-BASED HIGH-THROUGHPUT METHOD FOR SCREENING SMALL MOLECULES TO IDENTIFY REGULATORS OF HEPATITIS C VIRUS (HCV) REPLICATION *Sun Suk Kim[1], Lee F. Peng[1], Wenyu Lin[1], Won Hyeok Choe[1], Kyung-Ah Kim[1], Naoya Sakamoto[2], Stuart L. Schreiber[3], Raymond T. Chung[1]; [1]Gastrointestinal unit, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA; [2]Department of Gastroenterology and Hepatology, Tokyo Medical and Dental University, Bunkyo-ku, Japan; [3]Department of Chemistry and Chemical Biology, Harvard University, Boston, MA*

Background: About half of patients with HCV infection experience sustained virologic response to the current antiviral therapy, so the identification of more effective and better tolerated agents is a high priority. In parallel with advances in the cultivation of HCV, chemical biology has emerged as a powerful tool to study biological processes using small molecules. Aim: To develop a simple, reproducible, and reliable high throughput screening (HTS) assay system using a cell-based HCV replicon model in order to identify small molecules that regulate HCV replication. Methods: The components of a successful cell-based HTS assay include 1) a high density, automated screening technology platform, 2) a large and diverse collection of appropriate perturbagens, and 3) an appropriate replicon cell line having a tractable and reliable reporter system. We optimized the subgenomic Huh7/Reo-Feo (genotype 1b) replicon cells, which express luciferase as a reporter, to the 384-well plate format and then screened the 2568-member Kendall Bioactives library using automated technology. After identifying several molecules capable of either stimulating or inhibiting HCV replication, we validated our hits in a secondary screen using the full length OR-6 replicon cell in order to verify compound activity in a more authentic viral polyprotein context. As a counter-screen, cell viability was assessed in order to minimize falsely suppressed luciferase signals due to increased cell death and falsely increased luciferase signals due to increased cell proliferation. Results: We identified 21 antiviral compounds that inhibited HCV replication and 28 pro-viral compounds that increased HCV replication. The hit rates were 0.8% and 1.1%, respectively. Among the compounds whose activity was verified by the secondary assay, corticosteroids were found to stimulate HCV replication and the HMGR inhibitors were found to inhibit it. All of the HMGR inhibitors, except for pravastatin, significantly decreased HCV replication in dose-dependent manner with IC50 values between 1 and 10 μM. Conclusions: We have developed an efficient cell-based HTS assay system using HCV replicon model to identify small molecules that regulate HCV replication. This method can be used to identify not only putative antiviral agents, but also cellular regulators of replication. The finding of increased replication associated with corticosteroids suggests that these agents directly promote viral replication independent of their suppressive effects on the immune response. The finding of antiviral activity associated with the HMGR inhibitors suggests an important role for lipid metabolism in the viral lifecycle.

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CURRENT STATUS OF SUBJECTS RECEIVING PEG-INTERFERON-ALFA-2A (PEG-IFN) AND RIBAVIRIN (RBV) FOLLOW-ON THERAPY AFTER 28-DAY TREATMENT WITH THE HEPATITIS C PROTEASE INHIBITOR TELAPREVIR (VX-950), PEG-IFN AND RBV *Maribel Rodriguez-Torres[1,2], Eric Lawitz[3], Andrew Muir[4], James Keane[5], Tara Kieffer[5], Lindsay McNair[5], John G. McHutchison[4]; [1]Fundación de Investigación de Diego, Santurce, Puerto Rico; [2]Ponce School of Medicine, Ponce, Puerto Rico; [3]Alamo Medical Research, San Antonio, TX; [4]Duke Clinical Research Institute & Division of Gastroenterology, Durham, NC; [5]Vertex Pharmaceuticals Incorporated, Cambridge, MA*

Purpose: Telaprevir (VX-950) is an orally administered, highly selective peptidomimetic inhibitor of the Hepatitis C virus (HCV) NS3-4A protease. In previously reported Phase 1b studies, telaprevir was well tolerated alone and with peginterferon-alfa-2a (Peg-IFN) for 14 days, and the marked antiviral effects of telaprevir are increased with the addition of Peg-IFN. This study was designed to assess the safety of telaprevir when given in combination with Peg-IFN and ribavirin (RBV) and to evaluate the antiviral response during 28 days of dosing. Here we report patient status during ongoing post-study follow-on therapy. Methods: The VX05-950-102 clinical study included 12 treatment-naïve patients infected with genotype 1. All subjects received telaprevir (750 mg q8h), Peg-IFN (180 μg weekly), and RBV (1000 or 1200 mg daily). At the completion of the 28 days, patients began off-study follow-on standard therapy with Peg-IFN/RBV. Results: Telaprevir/Peg-IFN/RBV was well tolerated in this 28-day study, with no serious adverse events. The adverse event profile was consistent with the profile commonly seen with Peg-IFN/RBV therapy. All subjects demonstrated a response to the study drug regimen, with 2 subjects reaching undetectable ($<$ 10 IU/mL, Roche Taqman® Assay) levels of plasma HCV RNA within 8 days of the start of dosing, and all subjects HCV RNA-undetectable at the end of the 28-day dosing period. All subjects showed continual declines in HCV RNA throughout the dosing period, with no viral breakthrough. Viral sequencing analysis revealed viral variants in two subjects early in dosing; HCV RNA levels continued to decline to undetectable levels in both subjects by Day 22. At 12 weeks of follow-on therapy after completing the 28-day study dosing, 11 subjects had undetectable HCV RNA. Viral sequencing at the time of Peg-IFN/RBV breakthrough is in progress for the subject with detectable HCV RNA. All subjects are continuing on Peg-IFN/RBV therapy, and are being followed for response in accordance with standard practice; antiviral response through treatment week 42 will be presented. Conclusions: Telaprevir/Peg-IFN/RBV was well tolerated for 28 days in patients with HCV genotype 1. A rapid and substantial antiviral effect of telaprevir was observed, with all subjects achieving undetectable plasma HCV RNA within 28 days of dosing. Although viral variants were detected in two subjects, the subjects continued to respond and HCV RNA remained undetectable in both subjects after 12 weeks of follow-on therapy. Eleven subjects maintained undetectable HCV RNA through the first 12 weeks of post-study standard therapy.

Disclosures:
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