



**HEP DART™ 2011**  
frontiers in drug development for viral hepatitis

**Satellite Mini-symposium**

# Curative Therapies for HCV: Resistance is Futile

**Grand Hyatt Kauai, Koloa, Kauai, HI**

**SUNDAY, DECEMBER 4, 2011**

- 9:00 Opening Remarks by the Chairs  
Robert Murphy, *Northwestern University, USA*  
Eugene Schiff, *University of Miami, USA*
- 9:10 Boceprevir in the era of DAA  
Fred Poordad, *Cedars-Sinai Medical Center, USA*
- 9:30 Resistance in the age of HCV protease inhibitor/pegIFN/RBV therapy  
Ann Kwong, *Vertex Pharmaceuticals, USA*
- 9:50 Interferon free therapy for HCV  
David Nelson, *University of Florida, USA*
- 10:10 Multiple approaches for a common goal  
Douglas Dieterich, *Mount Sinai School of Medicine, USA*
- 10:30 Break
- 11:00 Combination DAA strategies to cure HCV  
Douglas Mayers, *Idenix Pharmaceuticals, USA*
- 11:20 The host targeting cyclophilin inhibitor alisporivir presents a high barrier to resistance both *in vitro* and in HCV patients with no cross-resistance to DAAs  
Kai Lin, *Novartis, USA*
- 11:40 Advances in HCV viral load testing  
Gavin Cloherty, *Abbott Molecular, USA*
- 12:00 Gaps in future HCV therapies  
Michael Fried, *University of North Carolina at Chapel Hill, USA*
- 12:20 Lunch

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# Boceprevir in the era of DAA

**Fred Poordad**

*Cedars-Sinai Medical Center, USA*

The evolution of therapy in the treatment of hepatitis C is now progressing at a rapid pace. Ribavirin, the first oral agent used with interferon-based therapy, was developed over a decade ago. Two additional oral agents have been introduced into the treatment arsenal in 2011. These first two agents are protease inhibitors, directly acting on viral replication and greatly improving sustained response rates in genotype 1 hepatitis C. Others will follow over the next few years, but these agents are historic in setting the stage for other advances in the field.

Both telaprevir and boceprevir were approved in mid-2011 for the treatment of genotype 1 chronic hepatitis C. The overall sustained response rates in treatment naïve patients range from 63-75% and from 30-85% in treatment experienced patients. The improved efficacy is somewhat offset by the higher adverse event profile compared to pegylated interferon and ribavirin. The primary adverse events are anemia with both drugs, dysgeusia with boceprevir and rash and anorectal adverse events with telaprevir.

The field of HCV therapy will rapidly evolve over the next 3 years, and patient selection for treatment with currently available protease compounds versus awaiting treatment with future regimens will require an individualized approach to optimize outcomes and minimize the development of resistant variants, and contain healthcare expenditure.

# Resistance in the age of HCV protease inhibitor/pegIFN/RBV therapy

**Ann D. Kwong**

*Vertex Pharmaceuticals, Inc, Cambridge, MA, USA*

Variants with decreased sensitivity to direct acting antiviral drugs (DAA) are thought to exist at baseline (before treatment with antiviral therapy) due to the combination of a high viral replication rate and high error rate of the HCV replication machinery. Before treatment with a DAA, wild type (WT) virus predominates due to a decrease in replicative fitness for most resistant variants. The goal of HCV antiviral therapy is sustained virological response (SVR), which requires sustained inhibition of replication and elimination of drug-susceptible and drug-resistant variants. The addition of a DAA results in the inhibition of all virus that are sensitive to the concentration of the antiviral therapy. In the absence of complete suppression, DAAs may select for pre-existing variants with decreased DAA susceptibility, resulting in virologic failure. The phenotype of the resistant variant is a pharmacodynamic indication of the degree of antiviral pressure (e.g., level of the DAA) in the liver, which is the site of viral replication. Because of the morbidity associated with liver biopsies, the concentration of DAA in the liver cannot be directly measured. Thus, the phenotype of the variants escaping antiviral pressure is an indirect measure of the pharmacokinetic properties of the DAA in the liver. In the clinical development of INCIVIEK™ (telaprevir, TVR) a HCV protease inhibitor, a triple regimen containing telaprevir (TVR), a HCV protease inhibitor plus pegylated IFN alfa (P) and ribavirin (R) the identification and characterization of resistant variants helped to provide insight about viral dynamics below the limit of detection of standard HCV RNA assays. Furthermore, phenotypic characterization of variants helped define the role of TVR in suppressing WT virus and low levels variants and the role of PR in suppressing high-level resistant variants.

# Interferon free therapy for HCV: Interferon-free PSI-7977: Pan-GT Potency + High Barrier to Resistance = SVR

D Nelson<sup>1</sup>, E Lawitz<sup>2</sup>, EJ Gane<sup>3</sup>, CA Stedman<sup>4</sup>, RH Hyland<sup>5</sup>, WT Symonds<sup>5</sup>, R Hindes<sup>5</sup>, MM Berrey<sup>5</sup>

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PSI-7977, a potent uridine nucleotide analog entering Phase 3 development, has demonstrated high SVR rates in HCV GT 1, 2 and 3, in treatment regimens with and without IFN (PROTON, EASL 2011; ELECTRON, AASLD 2011). Additional clinical data are now emerging from the ATOMIC study in subjects with HCV GT4 or GT6 who received PSI-7977, and who have also achieved SVR. These consistently high SVR rates may be attributed to the inherent antiviral potency of PSI-7977, the consistent MOA as a chain-terminator independent of viral genotype, and the lack of resistant HCV variants capable of supporting replication *in vivo*. An additional element of PSI-7977's profile is exceptional tolerability and safety, with no drug discontinuations or related SAEs to date. Consistent viral kinetics have been observed across viral genotypes/subtypes in patients receiving PSI-7977 400 mg QD, independent of concomitant IFN or RBV administration, IL28B genotype, BMI, gender, and race/ethnicity. In ELECTRON, 10/10 GT2 or GT3 subjects receiving IFN-free PSI-7977 + RBV achieved RVR, and all achieved SVR12. The remaining 30 subjects who received PSI-7977 with 4, 8, or 12 weeks of interferon all achieved SVR12. No virologic breakthrough has been observed in any subject to date, regardless of HCV subgenotype, while receiving PSI-7977 400 mg in any clinical study. Across the Phase 2 program, >90% SVR has been observed in all patient populations receiving PSI-7977 400 mg QD with ribavirin, independent of interferon administration.

Conclusions: PSI-7977 400 mg QD elicits rapid declines in HCV RNA when administered with or without IFN. High on-treatment response and lack of viral breakthrough or resistance, even in the absence of interferon, ribavirin, or other potent DAA, confirms the clinically-relevant high barrier to resistance. Very low relapse rates in subjects across the PSI-7977 development program support the potency of the compound. The clinical antiviral efficacy in association with a promising safety profile supports the continued exploration of PSI-7977 with RBV or with another DAA in patients with all HCV genotypes.

# Multiple Approaches for a Common Goal: Data Overview on Pegylated Interferon Lambda, Daclatasvir and Asunaprevir

**Douglas Dieterich**

*Mount Sinai School of Medicine, New York, NY, USA*

With the newly approved telaprevir or boceprevir based treatment regimens for genotype 1 chronic hepatitis C, there are still about 25-33% genotype 1 naïve patients failing to achieve sustained virologic response (SVR), and SVR rates remain low in genotype 1 prior non-responders including null responders. In addition, treatment-induced anemia and dermatologic events are high. Interferon lambda induces antiviral activity via a signaling pathway similar to interferon alfa, but distinct receptors which are expressed primarily in epithelial cells and hepatocytes. Daclatasvir (DCV) is a first-in-class, highly selective HCV NS5A replication complex inhibitor with picomolar potency and broad genotypic coverage *in vitro*. Asunaprevir (ASV) is a selective inhibitor of the hepatitis C virus NS3 protease with antiviral activity against HCV genotype 1 and 4. Combination of DCV and ASV yielded additive to synergistic antiviral activity in the replicon system. This presentation will review the clinical trial data on pegylated interferon lambda in genotype 1, 4 and 2, 3 treatment naïve patients, and daclatasvir and asunaprevir with or without pegylated interferon alfa and ribavirin in genotype 1 null responders.

# Combination DAA strategies to cure HCV

**Douglas L Mayers and David N Standing**

*Idenix Pharmaceuticals, Cambridge, MA, USA*

The current standard of care with Pegylated-interferon (PegIFN), ribavirin (RBV) and an HCV protease inhibitor substantially improved response rates in HCV genotype 1 infected patients. Despite improved efficacy, these regimens have complex management schemes, significant side effects and result in drug resistant virus in patients who are not cured. Regimens that can cure HCV without the need for PegIFN are highly desirable and preliminary clinical data are encouraging. Preclinical data suggest that combinations of HCV direct acting antivirals (DAA) from different classes have the potential to produce antiviral synergy, to effectively inhibit intracellular HCV replication and to block the emergence of drug resistant virus. Potent combination regimens could potentially cure HCV without the need for PegIFN by an RNase H clearance mechanism. Whether ribavirin needs to be included in combination DAA regimens will require more clinical data as previous clinical trials of combinations without RBV have shown unacceptably high relapse rates.

Idenix Pharmaceuticals currently has two HCV DAAs in clinical development; IDX184, a nucleotide prodrug and IDX375, a non-nucleoside polymerase inhibitor and has ongoing drug discovery/development programs in several classes of HCV DAAs, including nucleotide prodrugs, HCV protease inhibitors and HCV NS5A inhibitors. We have focused on developing low milligram, QD/BID drugs with multi-genotypic HCV coverage and low potential for drug-drug interactions. Our ultimate goal is to have DAA components in a pan-genotypic PegIFN-free combination regimen to cure HCV. IDX 184, a prodrug of 2'-methyl guanosine monophosphate is our lead candidate in phase 2B evaluation. IDX184 shows potent, pan-genotypic activity *in vitro* with a high barrier to resistance emergence. Doses of 50 and 100 mg daily are currently in evaluation in combination with PegIFN/RBV. To date, the safety profile of IDX184/PegIFN/RBV is consistent with the profile seen with PegIFN/RBV alone.

IDX719, our preclinical NS5A inhibitor candidate, demonstrates IC50s of less than 25 pM against HCV GT 1-5 in the replicon system *in vitro* and is in advanced preclinical evaluation. We expect clinical testing to begin in early 2012. Over the past year, we have refocused our discovery efforts back into novel HCV nucleotide prodrugs, evaluating novel and existing prodrug mechanisms coupled to a variety of purine- and pyrimidine-containing nucleotides. These efforts have resulted in several interesting molecules which are under intensive preclinical evaluation. We believe that nucleoside/tide drugs will be a key component of future DAA combination regimens due to their pan-genotypic activity, low mg QD dosing, potent antiviral activity and high barrier to resistance.

# Host targeting cyclophilin inhibitor alisporivir presents a high barrier to resistance both *in vitro* and in HCV patients with no cross-resistance to DAAs

Kai Lin

Novartis, USA

With the introduction of direct acting antivirals (DAAs), rapid development of resistance has become a main concern for hepatitis C therapy. A complementary approach is to target host factors such as cyclophilins that are essential for viral replication and create a higher barrier to resistance. Alisporivir, a non-immunosuppressive cyclophilin inhibitor, is a promising first-in-class host targeting antiviral (HTA) with pan-genotypic HCV activity. As demonstrated *in vitro*, it was much more difficult to develop resistance to alisporivir compared to DAAs both in terms of the length of time required and the level of resistance obtained. Mutations associated with alisporivir treatment were mainly located in the domain II of NS5A, a proline-rich region that is a substrate of cyclophilin PPIase, which represents a distinct mechanism from those of DAAs. Indeed, there is no cross-resistance between alisporivir and DAAs including NS3 protease and NS5B polymerase inhibitors as well as NS5A inhibitors targeting domain I of NS5A, suggesting that these drugs can be used in combination. The most commonly selected mutation, D320E in NS5A, only slightly reduced the susceptibility to alisporivir (<3-fold). In a Phase IIb study with genotype 1 treatment naïve patients, alisporivir plus PEG-IFN- $\alpha$  and ribavirin showed a superior SVR (76%) with low viral breakthrough (2.8%). Genotypic and phenotypic analyses revealed that viral mutations and resistance did not appear to be the cause of viral breakthrough, which could be largely attributed to dose reduction or suboptimal exposure of the drugs. Furthermore, in an on-going phase II trial in genotypes 2 and 3 patients, alisporivir and ribavirin resulted in undetectable HCV RNA in almost half of the patients by week 6 as an IFN-free regimen. Taken together, both *in vitro* and clinical data suggest that alisporivir, currently in Phase III clinical trials, presents a high barrier to resistance and may play an essential role in future combination therapy for HCV.

# Advances in HCV viral load testing

**Gavin Cloherty**

*Abbott Molecular Inc., USA*

In the 40 years since the discovery of the HCV virus the development of new and improved diagnostic tools has helped health agencies to safeguard the blood supply and physicians and researchers to study and treat this complicated and challenging disease. The development of nucleic acid based tests (NAATs) has enabled clinicians and researchers to accurately detect and quantify very low levels of HCV. These new PCR based technologies can reliably monitor viral kinetics across a broad dynamic range providing an accurate picture of a patient's response to therapy. These results help physicians manage patients on therapy, predict clinical outcomes, adjust therapy duration and to avoid the development of drug resistance. As a result of these advances and increasing clinical utility, HCV viral load testing has become an integral part of the HCV treatment paradigm and is a central component of all new Direct Acting Anti-viral (DAA) therapeutic development programs.

There are a variety of commercially available HCV viral load assays utilizing different technologies. These differences result in performance characteristics that produce a range of results. Very little data exists on the impact that these performance characteristics may have on clinical trial outcomes and on patient management. This presentation will provide an overview on the relative performance characteristics of molecular diagnostic technologies employed in the diagnosis and monitoring of HCV and the potential impact on clinical trials and patient management.