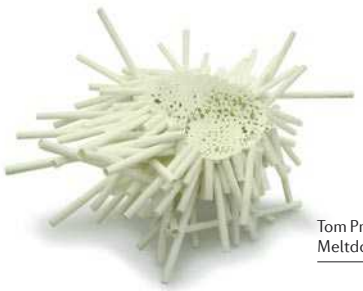
FROM THE ANALYST'S COUCH

Hepatitis C therapies

Irena Melnikova



Tom Price, Meltdown PP Tube

Hepatitis C virus (HCV) is the major cause of liver disease worldwide and a potential source of high morbidity and mortality in the future. The World Health Organization estimates that approximately 170 million people, 3% of the world's population, are chronically infected with HCV, and 3–4 million new infections occur each year. According to the Centers for Disease Control and Prevention, over 3 million people have chronic HCV in the US, and the current annual rate of infection is around 30,000.

The current standard of care for HCV is a combination of PEGylated–interferon (PEG–IFN) and ribavirin. PEG-IFNs available on the market include PEG–Intron (Schering–Plough) and Pegasys (Roche). Marketed ribavirin includes Rebetol (Schering–Plough), Copegus (Roche) and various generic versions. The overall clinical success rate, referred to as sustained virological response (SVR), of this combination therapy is only around 50%[1]. The treatment is lengthy (48 weeks for genotype 1 HCV) and associated with frequent and sometimes serious side effects including neuropsychiatric events, flu-like symptoms and haematological toxicities. It is also contraindicated for many patients[1]. Overall, it is estimated that only 10% of patients with chronic HCV are successfully treated with the current standard of care.

HCV pipeline

Over two dozen molecules are being studied for their potential to supplement or replace either or both elements of the standard PEG–IFN/ribavirin combination[2] (TABLE 1). Most of the efforts have focused on antiviral therapies, specifically two viral enzymes: the NS3–4A serine protease and the NS5B RNA-dependent RNA polymerase.

As evidenced by a number of high-profile partnerships with big pharma (TABLE 2), the HCV field has generated multiple value-creation opportunities for smaller biotech companies. Even preclinical programmes have received economics that are more typical of Phase II programmes (TABLE 2).

Protease inhibitors

NS3–4A protease activity is required for viral replication and is partially responsible for the ability of HCV to evade clearance by the immune system of the host. Therefore, protease inhibition could produce a double hit against the virus.

Telaprevir (VX-950; Vertex/Johnson & Johnson/Mitsubishi) is the most advanced novel anti-HCV therapy in development. In the clinical trials conducted so far, telaprevir has demonstrated unprecedented antiviral activity, offering hope for improved efficacy and reduced duration of treatment (24 weeks). Furthermore, telaprevir is the first drug to demonstrate activity in patients who have failed prior therapy. Interim analysis of the Phase IIb PROVE3 trial showed that 52% of patients treated with a 24-week telaprevir-based regimen maintained HCV RNA levels that were undetectable 12 weeks post-treatment (SVR 12)[3]. Patients who have previously failed standard-of-care treatment represent a significant market opportunity, and Vertex plans to initiate Phase III development in this setting. However, telaprevir is expected to be approved for the treatment-naive population first. A 24-week, Phase III trial of telaprevir compared with current standard treatment in treatment-naive patients with genotype 1 HCV is ongoing. If successful, approval in this setting is anticipated in late 2010/early 2011.

Although telaprevir has the potential to be first to market, there is an increasingly large number of competitive protease inhibitors in development — for example, boceprevir (Schering–Plough), ITMN-191 (InterMune/Roche) and TMC435350 (Tibotec/Medivir) (TABLE 1) — that may offer better tolerability and more convenient dosing (once a day versus three times a day) compared with telaprevir. However, superior efficacy and reduced duration of treatment are expected to remain major drivers for the adoption of new drugs.

Polymerase inhibitors

The concept of polymerase inhibition for antiviral therapy has been successfully established for HIV, hepatitis B and herpes viruses. Unfortunately, so far, tackling HCV polymerase has proved to be challenging. Several polymerase inhibitor programmes have been discontinued owing to lack of efficacy and/or safety issues. These include valopicitabine (Idenix Pharmaceuticals/Novartis), R803 (Rigel Pharmaceuticals), XTL-2125 (XTL Biopharmaceuticals) and HCV-796 (ViroPharma/Wyeth).

Nevertheless, several new polymerase inhibitors are progressing through the pipeline (TABLE 1). Roche currently holds a lead position with two compounds, R1626 and R7128; R7128 is licensed from Pharmasset. Experts suggest that out of the two, R7128 might have a more attractive profile as it has been well tolerated so far, whereas R1626 has been associated with fairly significant haematological toxicity (neutropaenia). In treatment-naive patients, R7128 has produced a rapid virological response in comparison with telaprevir when used in combination with standard of care: 85% and 79% of patients, respectively, achieved undetectable levels of HCV RNA after 4 weeks of treatment[4]. Whether the potent antiviral activities of the new generation of polymerase inhibitors will translate into a clinical benefit remains to be seen for a large majority of the compounds in the pipeline.

Other targets

Similar to HIV, the future of HCV therapy is likely to involve combination therapy with novel drugs that have different modes of action[5]. In the short-term, such drugs would be added to the current IFN-based regimen (FIG. 1). With time, potent antiviral combinations could displace IFNs altogether. However, lessons learned from the HIV epidemic suggest that owing to the high heterogeneity and high mutation rate of HCV, drug resistance is likely to emerge during treatment with specific inhibitors of viral protease and polymerase even in a combination setting[5]. Therefore, exploring additional targets that are vital for various stages of the viral life cycle remains important.

Several cyclophilin inhibitors, such as Debio-025 (Debiopharm), NIM811 (Novartis) and SCY-635 (Scynexis), are in Phase I/II clinical trials. Cyclophilin has been demonstrated to be an important host factor that supports HCV replication. Another potentially promising approach to treating HCV infections would be the inhibition of viral entry into the cell. XTL Biopharmaceuticals, Replicor, Progenics Pharmaceuticals, Samaritan Pharmaceuticals and Trimeris have early stage HCV fusion/entry inhibitor programmes. ▸

HEPATITIS C THERAPIES | MARKET INDICATORS

In the next 5–10 years, novel therapeutics are expected to produce major breakthroughs in the treatment of HCV, such as increased cure rates, reduced duration of therapy, improved tolerability/side effect profiles and more convenient dosing schedules and routes of administration (oral therapy). Furthermore, an increased number of patients is expected to seek treatment owing to advances in therapy.

The current cost of 48-weeks of therapy is approximately US$35,000. Introduction of novel anti-HCV drugs that will be used in combination with PEG–IFN/ribavirin could double or even triple the full cost of treatment. Therefore, the HCV market is projected to grow from over $2 billion in 2007 to $10–15 billion in 2017.

Irena Melnikova, Ph.D., is a Senior Associate at TVM Capital, 101 Arch Street, Boston, Massachusetts 02110, USA.
e-mail: melnikova@tvm-capital.com

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FURTHER INFORMATION
Clinical trials.gov: www.clinicaltrials.gov
Medline Plus Health Topics Hepatitis C: http://www.nlm.nih.gov/medlineplus/hepatitisc.html
ALL LINKS ARE ACTIVE IN THE ONLINE PDF

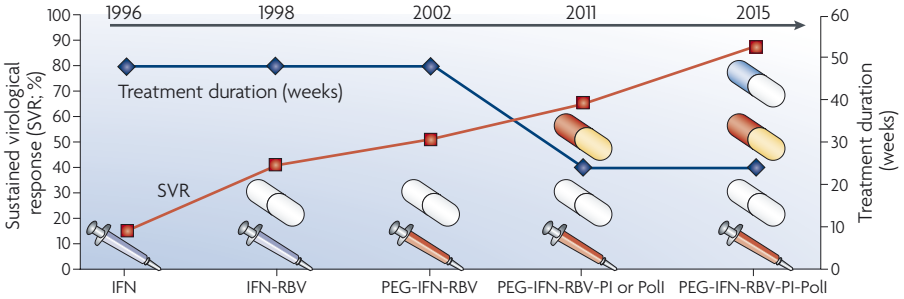

Figure 1 | **Evolution of HCV therapy.** IFN, interferon; PEG, pegylated; PI, protease inhibitor; PolI, polymerase inhibitor; RBV, ribavirin.

Table 1 | **Selected HCV drugs in development**

Company	Programme	Class	Status
Human Genome Sciences/Novartis	Albuferon	Long-acting albumin–interferon-α2b fusion	Phase III
Biolex	Locteron	Long-acting, controlled release interferon-α	Phase II
Valeant Pharmaceuticals	Taribavirin (viramidine)	Pro-drug of ribavirin	Phase IIb
Vertex/Johnson & Johnson/Mitsubishi	Telaprevir (VX-950)	Protease inhibitor	Phase III
Schering–Plough	Boceprevir (SCH503034)	Protease inhibitor	Phase II
Tibotec/Medivir	TMC435350	Protease inhibitor	Phase IIa
InterMune/Roche	ITMN-191	Protease inhibitor	Phase Ib
Boehringer Ingelheim	Second-generation protease inhibitor	Protease inhibitor	Phase I/II
Enanta/Abbott	EP-B, -G, -H	Protease inhibitor	Preclinical
Roche	R1626	Polymerase inhibitor	Phase IIb
Pharmasset/Roche	R7128	Polymerase inhibitor	Phase I
Gilead	GS 9190	Polymerase inhibitor	Phase I
Pfizer	PF868544	Polymerase inhibitor	Phase I
Merck	MK0608	Polymerase inhibitor	Phase I

Sources: Company information.

Table 2 | **Selected HCV partnerships**

Partnership (date)	Product	Mechanism of action	Stage	Deal structure
Human Genome Sciences/ Novartis (June 2006)	Albuferon	Long-acting albumin–interferon-α2b	Phase II	• Upfront $45million, milestones $507.5million • 50:50 split on US profits • Royalties on ex-US sales
Vertex/Johnson & Johnson/Mitsubishi (June 2006)	Telaprevir (VX-950)	NS3–4A protease inhibitor	Phase II	• Upfront $165million, milestones $380million • Fund 50% of development costs • Mid-20% royalties on ex-US sales, excluding Japan and Asia
InterMune/ Roche (October 2006)	ITMN-191	NS3–4A protease inhibitor	Preclinical	• Upfront $60 million, milestones $470 million • Fund 67% of development costs • 50:50 split on US profits, royalties on ex-US sales
Enanta/ Abbott (December 2006)	No named compounds	NS3–4A protease inhibitor	Preclinical	• Upfront $57 million, milestones $250 million for one compound, more milestones for additional compounds • Double-digit royalties • Option to fund 40% of development costs in exchange for 40% of profits

Sources: Company information