Evaluate Vantage

August 12, 2016

Therapy focus – Hepatitis B developers try to repeat Gilead's hep C trick

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When Roche pulled out of an alliance with Inovio two weeks ago to develop a hepatitis B treatment, it might have seemed like the Swiss giant was calling time on a disease that already had approved therapies in addition to a 95%-effective vaccine.

Nothing could be further from the truth, and a search of *EvaluatePharma* reveals Roche to be one of the most prominent developers of hepatitis B therapeutics (see table below). It is not the only big gun that sees potential here – Gilead and Johnson & Johnson are also active, as are several small biotechs whose investors will be keenly awaiting the outcome of mid-stage trials.

Undoubtedly the reason behind this excitement is the market's desire to find the next disease similar to hepatitis C. Development of a functional hep C cure with the drugs Sovaldi and Harvoni turned Gilead from a big biotech into a huge one whose market cap now outstrips that of Lilly and AstraZeneca.

While clearly there are similarities between hep B and C, the former has vaccines, and many infected patients are in the developing world. Acutely infected patients often recover spontaneously, but chronic infection can cause liver cirrhosis, and hep B is actually seen as harder to treat than hep C.

Approved current treatments for hep B comprise interferon and old HIV antivirals, implying side effects and no curative efficacy – viral replication can be suppressed but patients must be treated chronically. Several companies are working on novel prophylactic hep B vaccines, but this analysis looks only at treatments for already infected patients.

Mechanisms

Unfortunately Roche has not disclosed the mechanisms behind its three clinical-stage hep B antivirals, RO6864018, RO7020322 and RG7834.

Presumably it saw more promise in these than in Inovio's INO-1800, a DNA vaccine aiming to stimulate an immune response against surface and core antigens (*Inovio gets the final farewell from Roche, August 4, 2016*). Therapeutic vaccines are also being pursued by Transgene – with a large fusion protein comprising a core, polymerase and envelope domains – Altimmune and Aicuris.

However, the most important contender in hep B therapeutic vaccines is Gilead itself, with GS-4774, a project licensed from Globeimmune and in phase II in treatment-naive patients. A phase II study in virally suppressed subjects failed last year.

In phase II Gilead also has GS-9620, one of several small molecules in development. This agonises toll-like receptor 7, based on the theory that this stimulates an interferon response critical to developing broad, protective immunity; Roche also had a TLR7 agonist, ANA773/RG7795, but this completed phase II and has not appeared in the Swiss group's pipeline since 2012.

Hepatitis B therapy pipeline				
Project	**Company**	**Pharmacology**	**Trial ID**	**Data due?**
Phase II				
GS-9620	Gilead Sciences	TLR7 agonist	NCT02166047 & NCT02579382	Imminent & Dec 2016
GS-4774	Gilead Sciences/Globeimmune	Therapeutic vaccine	NCT02174276	Imminent
Myrcludex B	Hepatera	Viral entry inhibitor	NCT02637999	Imminent
REP 2139	Replicor	HBsAg release inhibitor	NCT02726789	Sep 2016
ARC-520	Arrowhead Pharmaceuticals	RNAi therapeutic	NCT02604199 and 4 others	Oct 2016
ARB-1467	Arbutus Biopharma	RNAi therapeutic	NCT02631096	Oct 2016
CMX157	Chimerix/Contravir	NNRTI	NCT02710604	Oct 2016
GC1102	Green Cross (Korea)	Recombinant hep B immunoglobulin	NCT02569372	May 2017
RO6864018	Roche	Not disclosed	NCT02391805	Sep 2017
SB 9200	Spring Bank Pharmaceuticals	RIG-I & NOD2 activator	NCT02751996	Dec 2017
REP 2165	Replicor	HBsAg release inhibitor	NCT02565719	Sep 2018
Phase I				
NVR 3-778	Johnson & Johnson	Capsid inhibitor	NCT02401737	Imminent
JNJ-56136379	Johnson & Johnson	Not disclosed	NCT02662712	Nov 2016
IONIS-HBV-LRx	GlaxoSmithKline/Ionis	Hepatitis B antisense	NCT02647281	Nov 2016
HepTcell (FP-02.2)	Altimmune	Therapeutic vaccine	NCT02496897	Feb 2017
RO7020322	Roche	Not disclosed	NCT02604355	Apr 2017
ARC-521	Arrowhead Pharmaceuticals	ccc DNA-targeting RNAi	NCT02797522	Jun 2017
TG1050	Transgene	Therapeutic vaccine	NCT02428400	Mar 2018
INO-1800/RG7944	Inovio Pharmaceuticals	Therapeutic vaccine	NCT02431312	Dec 2018
RG7834	Roche	Not disclosed	–	(1st pt in Q4 2015)
AIC649	Aicuris	Therapeutic vaccine	–	–
EYP001	Enyo Pharma	Farnesoid X receptor agonist	–	–
GSK3228836	GlaxoSmithKline/Ionis	Hepatitis B antisense	–	–
Source: EvaluatePharma and Clinicaltrials.gov.				

Hep B might be a tough nut to crack, but it actually presents many different targets, which explains the variety of mechanistic approaches being employed against it. Either the host can be targeted – this is the goal of TLR7 agonists and therapeutic vaccines – or the virus itself.

Hepatera's Myrcludex B, for instance, aims to prevent entry of the virus into the host cell, while other approaches attempt to hit viral processing such as encapsidation or replication, or secretion of HBsAg, a viral protein detectable in the blood of acute and chronic hep B patients; Replicor's REP 2139 and REP 2165, and Spring Bank's SB 9200 all ultimately target HBsAg.

J&J last year bought Novira, a private US biotech whose small molecule NVR 3-778 is a capsid inhibitor. Meanwhile another private biotech, Enyo Pharma, is developing EYP001, a farnesoid X receptor agonist aiming to hit another aspect of viral processing – the formation of covalently closed circular DNA (cccDNA), which is thought to act as a reservoir of infection.

Also targeting cccDNA is Arrowhead's ARC-521, though like Arbutus's ARB-1467 this is an RNA interference project. For small company watchers these and the related approach of RNA-targeted antisense, where Ionis has two phase I assets over which GlaxoSmithKline has an option, might be a particular focus.

Arrowhead recently started Monarch, one of six phase II trials of its lead asset, ARC-520, which it says interferes at the mRNA level upstream of the reverse transcription process. Interestingly, it was Roche that, for next to nothing, sold Arrowhead its RNAi technology back in 2011 (*EP Vantage interview – Arrowhead looks to evolve beyond the chimp, November 1, 2013*).

The Swiss group might have given up on RNAi and on Inovio's vaccines, but it certainly has not given up on hep B.

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