Evaluate Vantage

November 01, 2013

EP Vantage interview – Arrowhead looks to evolve beyond the chimp

Jacob Plieth

Arrowhead Research, a company built on an RNAi technology cast off by Roche, and whose biggest success so far has come from a trial in a chimpanzee, would likely not have risen 200% this year had this achievement not coincided with the US biotech bubble.

Its chief executive, Chris Anzalone, freely accepts that the market is frothy. But he also insists that the Roche technology is "the best thing we've ever seen" in RNAi, and is perfectly suited to hepatitis B, an intractable target that he says could become the next frontier in antiviral therapy.

The Roche business was acquired in 2011, and as far as Arrowhead's current focus goes "everything we have is based on those assets", he tells *EP Vantage*. The company's own RNAi technology "couldn't hold a candle to the Roche system".

Unfulfilled potential

The trouble is that RNAi – RNA interference, the idea of using short RNA molecules to bind to specific mRNA sequences and thus silence gene expression – has not fulfilled early potential, and one of the biggest problems has been how to deliver RNA fragments into cells.

But Mr Anzalone believes targetability, along with tolerability and efficient exit out of the cell, are the most important advantages of Roche's technology, which uses so-called dynamic polyconjugates specifically designed to overcome barriers to systemic administration. "Our big value driver is delivery."

And the first proof of Arrowhead's platform will be hepatitis B, the viral infection transmitted by exposure to blood or body fluids that Mr Anzalone says is "tailor-made" for RNAi. This is because there exists a specific gene product – a viral envelope protein called the S antigen – that can be knocked down, reducing viral load.

A few weeks ago the company reported that an ongoing volunteer study of its lead candidate, ARC-520, yielded no tolerability problems. "We were confident of the mechanism, so the real unknown was toxicity," says Mr Anzalone.

The breakthrough had come earlier in a chimpanzee that had had chronic hepatitis B for 34 years with multiple antiviral drugs and therapeutic vaccines tested on it, to no avail. Only three chimps in the world are known to be chronically infected with hepatitis B, says Mr Anzalone, "and we got to study one".

Despite the animal's extremely high viral load and extensive prior antiviral exposure, ARC-520 elicited long knockdown of viral antigens – something no one had ever shown before – raising hopes of a functional cure for the disease. The group's stock is up 227% year to date, largely on the back of this belief.

Suspicions

Still, it is fair enough to be suspicious of a technology Roche was happy to cut loose for nothing more than a 10% equity stake plus milestones and royalties. If it was so good, why was it jettisoned?

The answer, says Mr Anzalone, lies in the departure four years ago of the Swiss group's head of global research, Lee Babiss, who had championed RNAi. Until then Roche had spent some $500m trying to emulate Merck & Co's 2006 acquisition of the RNAi specialist Sirna Therapeutics for $1.1bn.

But Roche's plans hit the rocks when a project failed to make it into the clinic because of toxicology problems, and the final straw came when new management cut R&D funding. Mr Anzalone thinks Roche still had faith in the technology, otherwise it would not have retained rights to first negotiation.

And what about hepatitis B? On the face of it the choice of a disease that is largely confined to the developing world, for which a 95%-effective vaccine exists, and from which most acutely infected people recover spontaneously seems odd.

Be that as it may, the chief executive says the real target is the pool of chronically infected patients for whom a vaccine is of no help. He points to research estimating that there might be 2 million people with chronic disease in the US alone.

This makes for an interesting comparison with the red-hot area of hepatitis C, which according to Gilead Sciences counts 4.1 million infected US patients, 1.7 million of whom have been diagnosed.

Poor relation

But while hepatitis C is widely viewed as a multi-billion-dollar area, hepatitis B is at best its poor relation, and has almost completely failed to capture big pharma's interest. Current treatments basically comprise interferon and old HIV antivirals, implying terrible side effects and lack of efficacy.

Mr Anzalone does not find this unusual. "Hepatitis B is a very difficult virus," he says, adding that the industry has long been preoccupied with hepatitis C, "an easier nut to crack", and HIV. The bull case must be that this is about to change.

Arrowhead plans to start a placebo-controlled phase IIa efficacy study of ARC-520 in Hong Kong early next year. “We’ll be looking for deep and durable knockdown,” says Mr Anzalone. Thanks to last month’s $60m equity raise the group is funded until the expected readout of a further phase IIb trial in mid-2015.

“After hepatitis C people are asking what’s next, and many are turning to hepatitis B,” he adds. Time will be of the essence: with an opportunity to treat a finite pool of patients, “in 30 years it won’t be a huge market”.

To contact the writer of this story email Jacob Plieth in London at jacobp@epvantage.com or follow @JacobEPVantage on Twitter

More from Evaluate Vantage

Evaluate HQ
44-(0)20-7377-0800

Evaluate Americas
+1-617-573-9450

Evaluate APAC
+81-(0)80-1164-4754

© Copyright 2021 Evaluate Ltd.