BIOBUSINESS BRIEFS

DEAL WATCH

GSK invests in targeting microRNA for the treatment of hepatitis C

GlaxoSmithKline (GSK) has established a collaboration with Regulus Therapeutics to develop and commercialize therapeutics targeting microRNA-122 for hepatitis C virus (HCV) infection. Although a clinical development candidate has yet to be identified, recent findings in non-human primates indicate that targeting microRNA-122 blocks HCV replication and could offer advantages over current HCV therapies (*Science* 327, 198–201; 2010).

This deal, which could earn Regulus up to US$150 million in upfront payments and milestones, follows on from a 2-year-old, $600-million pact between GSK and Regulus aimed at finding microRNA-targeted therapeutics to treat inflammatory diseases. Regulus, a joint venture that was established by Alnylam Pharmaceuticals and Isis Pharmaceuticals in 2007 to develop therapeutics based on microRNAs, is now anticipated to identify a microRNA-122 antagonist for clinical development in the next 12 months.

microRNA-122 is expressed in the liver and has been shown to be a crucial endogenous host factor for the replication of HCV in both cell-cultured human liver cells and in the liver of infected chimpanzees. microRNA-122 silencing has been achieved using chemically modified single-stranded microRNA-specific oligonucleotides (*Science* 309, 1577–1581; 2005) or a locked nucleic acid (LNA)-based antagonist (SPC3649), developed by Santaris Pharma (*Science* 327,198–201; 2010).

A potential advantage of such molecules over those in development that target viral enzymes, such as the HCV protease, is that they should be less susceptible to viral resistance, says Phillip Zamore, Co-Director, RNA Therapeutics Institute, University of Massachusetts Medical School, USA, who is also an Investigator of the Howard Hughes Medical Institute and part of the scientific advisory board for Regulus. "Importantly, in the recent study of SPC3649-mediated sequestration of microRNA-122 in HCV-infected chimpanzees, deep sequencing analysis revealed that no viral genomes emerged with mutations in either of the two microRNA-122 binding sites," says Peter Sarnow, Professor in the Department of Microbiology and Immunology, Stanford University School of Medicine, USA, who discovered the effect of microRNA-122 on HCV. "Thus, mutations in the eight nucleotide seed matches to microRNA-122 in HCV do not arise to, for example, recruit another microRNA that could substitute for microRNA-122," he adds.

As with other therapeutics based on oligonucleotides, achieving effective delivery is a key challenge for microRNA-targeted therapeutics, says Zamore. "MicroRNAs may also have cellular functions that become more important in particular environmental or pathogenic situations," he adds. Indeed, like other microRNAs, microRNA-122 is predicted to target hundreds of mRNA species, and so antagonizing its function completely might lead to undesirable effects.

"However, it is not clear whether all features in microRNAs that contribute to target mRNA specificity are known," notes Sarnow. "Therefore, fewer off-target effects than expected may be observed. For example, localization or turnover of microRNAs, extra 3′-terminal nucleotide additions in mature microRNAs and precursor microRNAs could all contribute to target mRNA specificity. This might provide the potential to minimize off-target effects by targeting subpopulations of microRNAs. In addition, LNAs seem to be preferentially found in liver and kidney, and so the functions of microRNAs in other tissues are likely to be only minimally affected."