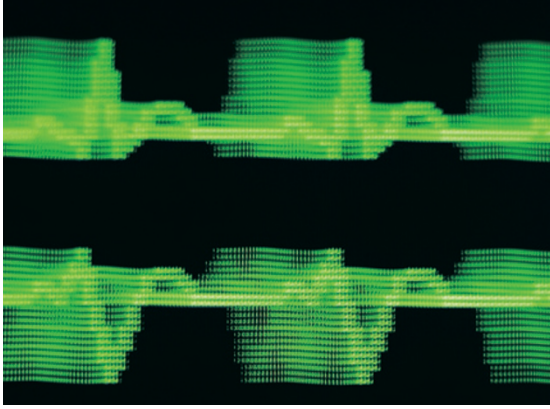
BIOBUSINESS BRIEFS



DEAL WATCH

MicroRNA collaboration to target cardiovascular disease pathways

Les Laboratoires Servier and MiRagen Therapeutics have agreed to jointly research, develop and commercialize three preclinical-stage oligonucleotide microRNA inhibitors — targeting microRNA-208 (miR208), miR-15/195 and an unidentified miRNA — for the treatment of cardiovascular disease. MiRagen will receive an upfront fee of US$45 million, with additional milestone payments and clinical development support from Servier valuing the deal at up to $1 billion. Servier will receive worldwide rights, excluding the United States and Japan.

MicroRNAs — small, non-coding single-stranded RNAs — bind to complementary sequences of mRNA transcripts and negatively regulate gene expression through repression of translation or destabilization of the mRNA, typically targeting multiple functionally related genes to control entire biological pathways. They are implicated in an increasing number of biological and disease processes and are therefore intriguing targets for therapeutic intervention. "Because microRNAs modulate collections of proteins within complex biological pathways, their therapeutic inhibition offers opportunities to modify disease processes in a manner distinct from that of classical drugs, which are typically directed at single cellular targets," explains Eric Olson, Professor and Chairman, Department of Molecular Biology, University of Texas Southwestern Medical Center, Dallas, Texas, USA, and co-founder of MiRagen.

MicroRNAs are recognized as important modulators of heart function and are dysregulated in various cardiovascular diseases. "Antagonizing specific microRNAs in cardiovascular disease is a tantalizing prospect, providing a potential opportunity to target a portfolio of disease-related genes," says Douglas Mann, Professor and Chief, Cardiovascular Division, Washington University School of Medicine, St Louis, Missouri, USA, and a member of MiRagen's scientific advisory board. "This has enormous theoretical appeal in terms of treating complex diseases such as heart failure, for which the development of new therapies has been limited due to our reductionist approach that targets isolated signal transduction pathways, many of which are redundant."

The microRNAs named in the deal are novel therapeutic targets — miR-208 appears to have an important role in the pathogenesis and progression of heart failure, whereas miR-15/195 have been implicated in the survival and proliferative capacity of cardiomyocytes — and preclinical data so far are encouraging. "miR-208 appears to be a particularly promising therapeutic target because it is cardiac-specific. In addition, there is solid validation of miR-208 as a mediator of cardiac dysfunction in response to stress, based on genetic deletion and microRNA inhibition in rodents," says Olson. "miR-15/195 have also been shown to be induced in the heart following myocardial infarction and to be sufficient to impede heart repair when upregulated. Recent *in vivo* inhibition studies of miR-15/195 with oligonucleotide inhibitors further highlight the involvement of these microRNAs in heart disease," he adds.

Although the excitement around RNA-targeted medicines has subsided in recent years — largely owing to specificity concerns, insufficient potency and delivery issues associated with double-stranded small interfering RNA (siRNA) agents — MiRagen has taken steps to address these challenges. It is using Santaris Pharma's locked nucleic acid (LNA) platform, which enables the production of short, high-affinity oligonucleotides that do not require complex delivery vehicles. "MicroRNA inhibitors modified by LNA technology are effectively taken up by the heart following subcutaneous delivery, and cause persistent inhibition of microRNA targets over periods of several weeks. The efficiency of uptake and target inhibition by these oligonucleotides appears to overcome many of the limitations associated with traditional siRNA approaches," says Olson.