

# Developing LNA technology for new-generation cancer drugs

*Danish biopharma company Santaris Pharma A/S was formed in 2003 with the aim of developing and exploiting locked nucleic acid (LNA) technology to produce more effective cancer treatments. Keith McCullagh, the company's CEO, describes the business's strategy and its progress to date.*



Keith McCullagh

Keith McCullagh is chief executive officer of Santaris Pharma, a Danish biopharmaceutical company dedicated to the discovery, development and commercialisation of new and improved drugs for the treatment of cancer and metabolic diseases. He joined the company in October 2003 following its creation through the merger in May that year of Cureon A/S and Pantheco A/S, two companies specialising in RNA antagonising technologies. Santaris has a number of innovative cancer drugs in development, each of which targets a

molecular mechanism known to be important in the development and progression of certain cancers. As such, each product has the potential to treat a different range of human cancers. In May of last year, the company's most advanced drug candidate, SPC2996, entered a multi-centre Phase I/II clinical study in patients with chronic lymphocytic leukaemia. Further clinical studies will follow with two additional drug candidates, SPC2968 and SPC3042, which are currently undergoing preclinical development.

## LNA technology

"Our development programmes are based on drugs derived from our proprietary RNA antagonist technology, termed Locked Nucleic Acid or LNA," says McCullagh. "Synthetic oligonucleotides can be rationally designed to specifically intercept RNA molecules of virtually any gene thereby preventing their expression into disease-causing proteins. As such, synthetic oligonucleotides provide a potential means of rapidly and cost-effectively translating the tidal wave of genomic discoveries into novel drugs against an increasing number of diseases."

Santaris Pharma holds worldwide exclusive rights for the exploitation of LNA technology in therapeutics. The new chemistry enables the development of oligonucleotides with very high target affinity and biostability: "We have termed such oligonucleotides 'RNA antagonists' to signal their potential to transform the future of oligonucleotide-based drugs," says McCullagh. "Leveraging the LNA platform in cancer, we are researching and developing RNA antagonists against genes that are central to tumour growth and malignant behaviour using both the antisense and siRNA principles.

"DNA- and RNA-based drugs are in themselves not very stable, so one approach to improve this is to modify the backbone to stabilise these molecules against nucleases. However, this makes them less potent. Santaris Pharma has

patented chemistry for the synthesis of locked nucleic acids, in which the ribose ring is locked into an RNA-like conformation to produce a synthetic analogue of RNA that binds RNA very tightly.

"Unlike nucleotides, the locked RNA is resistant to nuclease digestion, which can occur in human tissue and in the bloodstream. siRNAs can degrade in plasma in five or ten minutes, whereas locked nucleic acids have half lives of the order of days or even weeks. The molecules exhibit binding that is two or three times better than that obtained with conventional antisense molecules.

"Antisense drugs work at the gene level to interrupt or modulate the translation of a target mRNA into a protein. As such, antisense drugs have the potential to treat a diversity of human diseases that are caused by the production of inappropriate amounts, or mutated forms, of proteins," he says.

## New business structure supports new products

Following a restructuring, Santaris Pharma, with its new management team, is now looking to close a Series B funding in the order of €30 million. The company's first product, SPC2996, is now in clinical trials in Denmark, France, the UK and the USA: "We are looking at whether the molecule should be applied as a single-agent therapy or in a combination, and we are planning a second Phase I/II clinical trial later this year on the combination product," says McCullagh. "We'll look for drug/drug interactions as well as safety and efficacy data and will monitor the gene as a marker for the success of the treatment. The drug could be approved as early as 2009.

"Our second product is an HIF-1 $\alpha$  antagonist, which prevents the triggering of a range of genes associated with the spread of cancer. We have completed a primate chronic toxicology study on this product and expect to register it as an IND in the first half of this year. Our third product is SPC3042, an antagonist of survivin, a protein associated with mitosis. This drug works by blocking the progression of tumours. We expect to file for an IND for this product in the second half of the year.

"Investors and partners have shown more interest in our company as the efficacies of these products have been demonstrated. We will leverage our proprietary RNA antagonist drug platform by working with interested third parties on a licence basis and, where attractive, Santaris Pharma will boost its home-grown pipeline through in-licensing of complementary products. We believe our single-stranded RNA products represent a huge opportunity for the future," McCullagh concludes. <sup>sp<sup>2</sup></sup>

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