BIOWORLD™ TODAY
THE DAILY BIOPHARMACEUTICAL NEWS SOURCE
BIOTECH'S MOST RESPECTED NEWS SOURCE FOR MORE THAN 20 YEARS
DECEMBER 30, 2015
VOLUME 26, NO. 248
SPECIAL REPRINT

Synpromics takes gene therapy to the next level with synthetic versions

By Nuala Moran, Staff Writer

LONDON – Synthetic promoters – a new and controllable means of directing gene expression – are starting to be deployed to increase the potency and specificity of gene therapies and to boost yields in bioprocessing.

As one of the early fruits of synthetic biology, synthetic promoters are rationally designed to be specific and tunable replacements for the natural viral or endogenous promoters that the biotech industry relies on currently to regulate genes.

The man-made DNA sequences can control the activity of any gene of interest, mediating levels of protein expression that are significantly higher than is achieved with standard promoters. Each is patentable.

A leader in the field is Synpromics Ltd., which after completing several low-key assignments to validate the technology, in December signed two separate deals with Nasdaq-listed U.S. companies that are developing gene therapies for eye diseases.

In the first, Synpromics' ability to design specific promoters will be combined with Avalanche Biotechnologies Inc.'s ocular biofactory technology platform, which uses directed evolution to generate adeno-associated vectors (AAV) that are optimized for targeting different cell types in different layers of the retina.

The second agreement sees Edinburgh, Scotland-based Synpromics teaming up with Applied Genetic Technology Corp. (AGTC) to generate synthetic promoters that increase expression levels of AGTC's AAV-based gene therapies for treating rare eye diseases.

"At present everyone in the industry is using viral or endogenous promoters to drive gene function. We can go to our functional genomics database and mine for transcription sites and then custom design promoters for specific purposes," David Venables, CEO of Synpromics told *BioWorld Today*.

This includes activating gene expression in response to biological or chemical conditions, or in particular cell types. "With current viral vectors the gene is active wherever the vector is. We can limit activity to a cell type, for example, T cells or tumor cells, with no off-target expression in other cell types," Venables said.

It also is possible to dial up the level of expression and so lower the required dose of a gene therapy, or to create promoters that turn genes off and on in response to small-molecule inducers.

As a result, gene therapies "will go to another level in terms of potency and specificity," Venables claimed. For example, in ophthalmology it will be possible to create promoters that are active only in retinal pigment epithelial cells.

SMALL SIZE, BIG ADVANTAGE

Apart from specificity and higher expression levels, synthetic promoters offer a further advantage for developers of AAV-delivered gene therapies, which is their small size.

"AAVs are not high volume vectors. We have made promoters of 250 base pairs that are five times more productive than existing counterparts," said Venables. "For Factor VIII or other large genes, having a very small promoter is a huge benefit in terms of cost and overcoming the limitations of vectors."

In January 2015 Synpromics signed a deal with gene therapy specialist Uniqure NV to take advantage of these properties for products that require high levels of therapeutic gene expression or which involve the delivery of large genes. The work is focusing on gene delivery and expression in the liver.

Synpromics also has signed a research agreement with Dow Agrosciences to explore the use of synthetic promoters in the development of new traits in crops and in plant cell bioprocessing.

In 2014 Synpromics won a grant from the government innovation agency Innovate UK to produce promoters for mammalian cell culture bioprocessing. Venables said this research has shown it is possible to boost protein expression levels in Chinese hamster ovary cell lines by five to 10 times. The promoters also improved genetic stability and are suitable for use at an industrial scale.

ENHANCING DNA VACCINES

The company's most advanced project, using synthetic promoters in DNA vaccines, is about to enter animal testing.

Here, Synpromics is collaborating with another U.K. synthetic biology company, Touchlight Genetics Ltd., which is developing a technology for synthesizing DNA at high volumes without the use of bacterial expression systems. The aim is to design promoters that drive antigen expression in dendritic and keratinocyte cells as a way of enhancing the effectiveness of DNA vaccines.

The idea of interrogating functional genomics databases to find the source code for gene promoters is that of Michael Roberts, chief science officer and founder of Synpromics.

The synthetic promoters are put together from sections of natural promoters to form new pieces of DNA that do not exist in nature.

"We don't start with existing promoters and then tweak them; we start from scratch and build from libraries," Venables said. "Everything is patentable because it is synthetic, enhancing the patent position of partner companies."

A briefing document is being prepared by Synpromics to make the case for its promoters to the FDA and EMA. "Current products use viral promoters with no element of control. We are targeted and controllable: I would argue that will translate to better products," said Venables.

Synpromics closed its first formal venture capital round in August when it raised £2.1 million (US$3.1 million) from a single investor, Calculus Capital. For the four years before that it was financed by family and friends.

"Now we have got the finance we are building up the team in support of a pipeline of deals," said Venables. We have only been actively promoting since the start of 2015, but there is a lot of appetite. I think our technology hit a need with a solution at exactly the right time." //