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Progress For Non-Cutting CRISPR Technology

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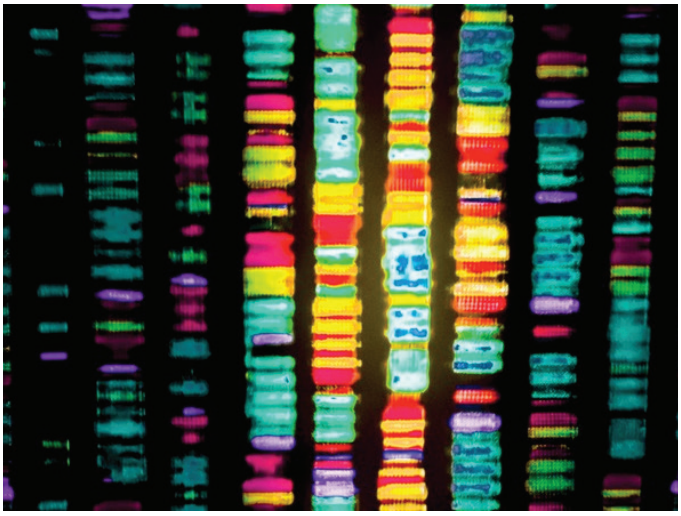

THE SAN FRANCISCO-BASED COMPANY HAS TAKEN a step forward with proof of concept for its ‘switch on or switch off’ approach to gene regulation via non-cutting CRISPR molecules.

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Epic Bio has presented early data from its non-cutting CRISPR technology which aims to overcome limitations of existing gene therapies and turn on or off disease-related genes.

The company was launched last July by CRISPR co-inventor Stanley Qi with a $55m backing from investors to develop its vision for ‘epigenetic engineering’ to tap into the body’s system for controlling gene expression.

The South San Francisco, CA-based biotech holds an exclusive license to a Cas enzyme called CasMINI, which it claims is the smallest and most deliverable dCas DNA-binding protein (ie, a catalytically inactive protein dead Cas9), at less than half the size of the most commonly used Cas9 or Cas12a endonucleases.

Existing gene editing platforms use Cas proteins to knock out disease-causing genes or otherwise insert healthy genes into the body, but many of these payloads are too big for AAV vectors, limiting their available targets.

By contrast, Epic’s compact CasMINI DNA-binding proteins can easily fit into AAVs and could enable Epic to deliver single AAV vectors to all tissues and organs, where they can then upregulate or downregulate gene expression.

The technology aims to turn genes on or off by delivering effectors to the desired sites in the genome for targeted transcriptional repression or activation, rather than using the CRISPR Cas9 ‘genetic scissors’ to cut out a faulty gene. The company believes it provides not only greater versatility but also greater reassurance on long-term safety, particularly on potential off-target effects.

Epigenetic editing does not directly alter DNA, which allows treatment to be reversible or more precisely dial gene expression up or down. This approach has particular promise in haploinsufficient diseases where the gene is present but not active enough to generate health levels of the required protein.

At launch, the company declared its lead program to be in one such condition, facioscapulohumeral muscular dystrophy (FSHD), the most common adult muscular dystrophy, for which there are currently no treatments available.

Proof-Of-Principle

Epic has now presented in vitro proof-of-principle data showing its Gene Expression Modulation System (GEMS) platform has achieved significant and sustained stimulation of a target gene.

Existing methods of penetrating cells and switching on genes include the use of HIV-derived VPR protein, but this has been shown to last for only 12 cell divisions, roughly six days, making it not durable enough for therapeutic purposes. Epic's new data showed that their construct had a greater magnitude and duration of effect of up to 80 cell divisions, or around 40 days.

That result is an important first step in the right direction, though the company concedes it needs to increase the magnitude of effect and duration to build a robust therapeutic platform.

Dan Hart

"These data are a thrilling proof-of-principle for our GEMS platform's ability to generate new therapeutic constructs that can overcome longstanding challenges within genetic medicine," said Dan Hart, the company's head of technology development.

"In this case those challenges were two-fold: no one has yet demonstrated epigenetic gene activators with more than a short-lived effect, and secondly, even those short-lived activators are too large to be packaged within a clinically validated AAV vector, limiting their use as in vivo therapies."

Another company active in the field is Chroma Medicine; its platform is using a chromatin control mechanism which mimics the cell's innate means of controlling gene expression.

Added To Down Regulation

The new data add to existing early in vitro data for FSHD unveiled in October. Epic's CasMINI constructs have been shown to downregulate the DUX4 gene responsible for the disease, cutting expression levels by 95%. This is backed by animal studies which showed that muscle cells were kept healthy in treated mice compared with those not receiving treatment.

The company filed a pre-IND briefing for its FSHD program with the US Food and Drug Administration late last year and the regulator has confirmed the company's plans for safety non-GLP studies.

Epic will initiate GLP safety studies in Q2 this year, which should lead on to an IND filing by the end of 2023, with the hope of first dosing in a Phase I study early next year.

There is already a candidate in Phase III development for FSHD, Fulcrum Therapeutics's losmapimod, a small molecule p38 α/β MAPK inhibitor.

The company's CEO Amber Salzman said Fulcrum had laid a lot of groundwork in establishing measurable endpoints and natural history in FSHD, which Epic would be able to leverage in its future studies. While Fulcrum's drug has so far only been shown to slow disease pro-

Amber Salzman

gression, Epic hopes its potential one-and-done gene therapy could transform outcomes for these patients.

Potential In Cholesterol Regulation

Epic also wants to home in on the advantage of having a transient effect, and sees the platform as a rival to other gene-therapy approaches.

Salzman said it was also investigating a novel approach to heterozygous familial hypercholesterolemia, with a mechanism that contrasts with existing approaches of blocking our editing out the PCSK9 protein. (Also see "Verve Hits The Clinic With Gene-Edited Cholesterol-Lowering Drug" - Scrip, 12 Jul, 2022.)

Instead, Epic's pre-clinical EP1-221 would upregulate the low-density lipoprotein receptor (LDLR) gene, which produces the protein which binds to low-density lipoproteins, the chief carriers of cholesterol. She said twinning that effect with a downregulation of PCSK9 would further boost the therapeutic effect.

"Nobody else can do that, and it's really thanks to Dan's team development of these very compact modulators," added Salzman. The company has three further pre-clinical programs: EPI-241 for alpha-1 antitrypsin deficiency, EPI-141 for retinitis pigmentosa 4 and EPI-111 for retinitis pigmentosa 11.

Fundraising In Tricky Times

The company is now in the midst of series B financing, which comes at a difficult time for pre-clinical biotechs to raise money. Nevertheless, Salzman was optimistic that investors would back its platform, and understand how its approach is distinct from other CRISPR or base-editing platforms, such as those from Beam Therapeutics and Verve Therapeutics. However, proof that Epic's approach could demonstrate clear safety and efficacy advantages over these more advanced platforms will still be years away.

At the same time, she pointed to the progress of ground-breaking companies such as Intellia which is now advancing into Phase II studies of its in vivo CRISPR gene-editing platform, as good news for the wider genetic medicines field.

She also highlighted the success of its epigenetics rival Chroma Medicine, which completed a $135m series B round in early March. (Also see "Finance Watch: VC Mega-Rounds Make A Comeback In March" - Scrip, 9 Mar, 2023.)