Synpromics

the leader in gene control

Recent technology advancements have enabled significant progress in the efficiency, efficacy, and safety of gene- and cell-based medicines for a multitude of genetic disorders. In particular, these advancements have improved gene delivery to disease-affected cell types. This means that product developers now must improve the gene expression cassette payload in response to the emerging importance of tight, targeted, and robust gene regulation.

Synpromics has developed a technology platform, PROMPT®, and a proprietary machine learning methodology to create libraries of promoter candidates that are designed and developed according to a discreet set of specifications, such as the size of the promoter; the tissue, cell or multiple cell type selectivity of the promoter; the strength of the promoter; and whether the promoter is constitutively expressed in the target cell type(s) or is regulated or inducible in the cell. These promoters can be designed for both in vivo or ex vivo applications. New promoters are required to drive efficient, yet finely tuned, gene expression so that the therapeutic effect is safe, directed, and durable and to minimize long-term immune responses to the therapeutic cassette.

Liver Gene Therapy: A Successful Collaboration with uniQure

In 2015, Synpromics embarked on a collaboration with uniQure, the first company to bring a gene therapy into the marketplace, to develop highly potent, liver selective promoters for gene therapy applications. uniQure had developed AAV5 as a tool to deliver gene payloads to the liver and is using it in a number of its clinical programs. However, they recognized that a collaboration with Synpromics would allow them to improve transcriptional targeting of hepatocytes through incorporating Synpromics promoter technology into their AAV5 platform, resulting in an improved safety and efficacy profile.

Short Potent Liver Promoters – Incorporation of Synpromics Technology into Clinical Candidates

Synpromics had designed and screened libraries of liver-selective promoter candidates over an eight-month period that showed remarkable strength and passed them onto the uniQure team. The remit was to create promoters that could mediate liver-selective gene expression five times more effective than the promoter that uniQure was using in its current gene therapies; initial testing in mice showed that the Synpromics lead promoter candidate was closer to 50 times more active than the previous industry standard (figure 1).

uniQure's new gene therapy aims to treat all patients with hemophilia A, one of the two main types of hemophilia. Hemophilia A is caused by missing or defective Factor VIII, a protein essential for clotting. Approximately 30 percent of patients with severe hemophilia A will develop an inhibitor that neutralises the infused Factor VIII (FVIII) activity. This patient population has, in the past, been excluded from gene therapy approaches in clinical development; however, uniQure's new candidate has been demonstrated in preclinical studies to circumvent inhibitors to FVIII. This data shows that the candidate may lead to durable expression in hemophilia A patients and may provide long-term prevention of bleeds. The promoter, developed by Synpromics, is a key component of this new candidate.

uniQure have continued to work on the other Synpromics promoters and, in April 2019, they presented data from their Fabry's disease program, announcing the use of another Synpromics promoter in its preclinical pipeline. The collaboration between the two companies continue to flourish and uniQure remain engaged as the two companies look to combine their respective platforms to improve genetic medicine in other disease indications.

Figure 1) Transfection vs Transduction vs *in vivo*

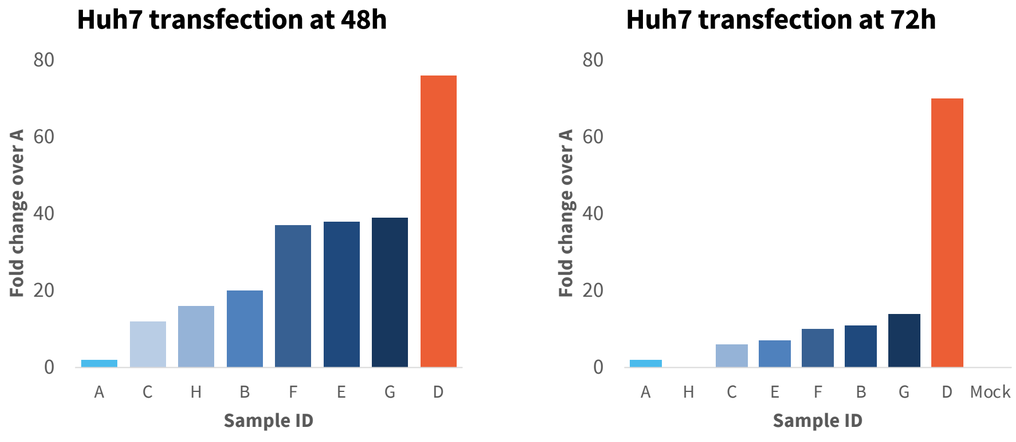

Figure 2) Therapeutic transgene validation in NHP

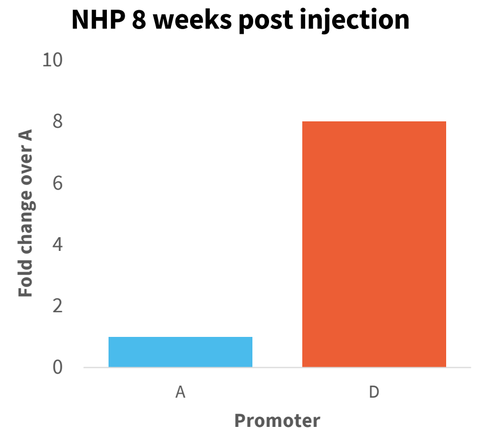

Figure 1 *shows that the Synpromics best candidate promoter (D) is more than 50 times stronger than uniQure's previous liver selective promoter.* ***Figure 2*** *shows that the Synpromics promoter (D) is more than eight times stronger than uniQure's previous liver selective promoter (A), when expressing the Super9™ gene in non-human primates.*

Alliance for Regenerative Medicine

BIA UK BioIndustry Association