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ENGENE

Pioneering oral delivery for gene therapy

enGene has developed a proprietary nonviral gene delivery platform and Gene Pill technology to deliver orally administered gene therapies to mucosal tissues, creating new opportunities for treating hard-to-reach tissues across many indications.

Mucosal tissues are challenging to treat using current delivery approaches for protein therapies. It is difficult to achieve a sufficient concentration of therapeutic protein at the intended target site without reaching the tipping point of systemic toxicities. Moreover, most biologics are degraded in the gut, well before they reach their target. enGene is taking a radically different approach to overcome these problems. By turning mucosal tissue cells into bioreactors of therapeutic effectors, such as proteins, peptides, antibodies, and short hairpin RNAs, the company aims to concentrate biologics exactly where they are needed.

"We have built a robust nonviral gene delivery platform, which can penetrate mucosal tissues and deliver a nucleic acid [NA] payload encoding a specific therapeutic protein, and have developed a solid dosage form for oral delivery with our Gene Pill technology," said Anthony Cheung, CTO and cofounder at enGene. "To the best of our knowledge, this is the most advanced platform for oral delivery of gene therapies."

Unlike virus-based gene therapies, the dosing of enGene's nonviral delivery vehicle is transient, owing to the rapid turnover of epithelial cells in mucosal tissues. It is also repeatable, titratable, and does not require systemic injections or infusions. No immunogenicity has been observed to date. The approach overcomes the capacity limitations typical for viral vectors, as it enables large and/or multiple genes to be delivered simultaneously. Reimbursement challenges are also expected to be significantly lower than for virus-based gene therapies. Importantly, enGene has successfully formulated its novel nonviral gene delivery vector into an oral solid dosage form without compromising its stability and potency.

Based in Montreal, Canada, and Boston, Massachusetts, enGene has a world-class leadership team and board. The company has been highly capital efficient and strategically focused in order to advance its proprietary mucosal gene delivery platform, including the development of a robust, scalable manufacturing process with a low cost of goods. enGene is initiating a financing campaign for a series C/crossover round and is open to partnering opportunities to advance the development of its assets.

Robust nonviral delivery vehicle

enGene has built a scalable plug-and-play gene therapy platform with the flexibility to deliver a wide range of payloads. The company's proprietary DDX polymer is coupled with high efficiency to a plasmid payload as part of a proprietary manufacturing process to create a dose-ready nanoparticle suspension.

With its DDX polymer, enGene has demonstrated the capability to deliver nucleotide sequences encoding proteins, peptides, and antibodies. The platform is also amenable to carrying RNA and oligo-NA payloads, thereby facilitating the delivery of messenger RNA, long noncoding RNA, small interfering RNA, microRNA, and aptamers. Additionally, the technology can be leveraged in partnerships with companies advancing gene-editing approaches.

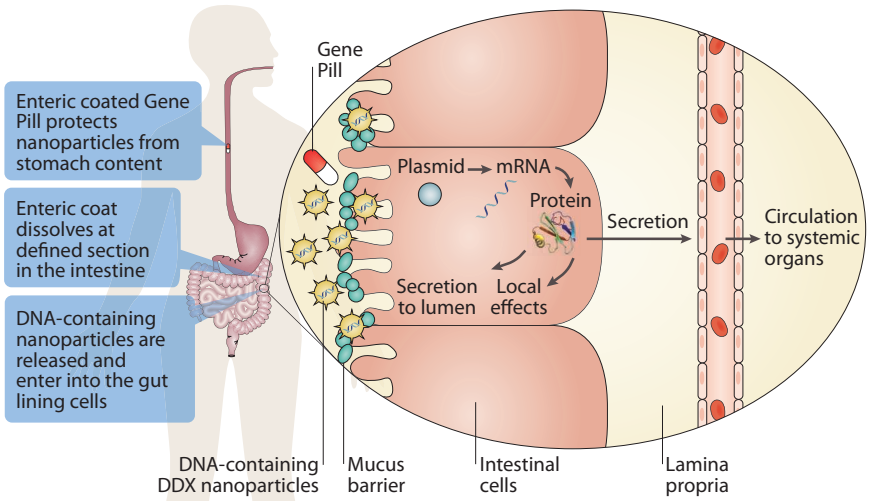

Fig. 1 | The Gene Pill. This system turns intestinal cells into 'bioreactors' that produce therapeutic proteins for local effects or for potential secretion into the circulation for systemic effects.

The DDX nanoparticle suspension can be converted readily into a Gene Pill for oral delivery via a second proprietary manufacturing process, without reducing transfection efficiency. Gene therapy companies that use viral vectors are unable to create solid dosage forms in this way, as viral vectors cannot withstand the process of generating an amenable solid dosage form.

Targeting mucosal tissues

The two formulation formats—suspension and solid oral dosage—enable enGene to target different mucosal tissues in the body. The powder-in-bottle DDX formulation can be rehydrated and delivered topically to mucosal tissues such as the lower colon (via enema) and the bladder (via intravesicular administration), whereas oral delivery with the Gene Pill can target specific sections of the gastrointestinal (GI) tract. By using different enteric coatings for the Gene Pill, it is possible to target defined sections of the GI tract for indications such as inflammatory bowel disease (IBD).

Once the Gene Pill has dissolved in the GI tract, it releases DDX nanoparticles, which are designed to overcome the challenges of penetrating the mucosal barrier (**Fig. 1**). enGene's nanoparticles are designed to pass through mucus layer pores, and a hydrophilic surface prevents them from becoming trapped in mucin (unlike hydrophobic lipid nanoparticles).

The target epithelial cells are then coaxed into becoming bioreactors to produce therapeutic protein (**Fig. 1**).

Partnering opportunities

enGene has demonstrated preclinical proof of concept for DDX nanoparticle suspensions and the solid dosage form of Gene Pill, and is planning to advance its pipeline of candidates to the clinic. These include a DDX nanoparticle suspension formulation for non-muscle-invasive bladder cancer, which is due to start investigational new drug (IND)-enabling studies later this year. The Gene Pill formulation is being developed for IBD and for short bowel syndrome, with IND filings for both indications anticipated in 2020.

"We have only scratched the surface of possibilities for our platform to date," said Cheung. "We can effectively formulate DDX to express any therapeutic protein in any accessible mucosal tissue. Efforts are underway to adapt our solid dosage form for inhalable delivery to the lungs, which would enable treatments for various pulmonary diseases, such as cystic fibrosis."

"There are many potential applications for our gene therapy platform, and we are open to discussing further partnering opportunities to develop these," said Jason Hanson, enGene's CEO.

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