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How Entos' delivery platform is realizing the untapped promise of genetic medicines

Unique proteolipid vehicle (PLV) technology developed by Entos Pharmaceuticals is broadening the scope for biopharma to deliver nucleic-acid payoffs to target cells throughout the body, paving the way for a new generation of curative drugs.

The genetic-medicine revolution is incomplete. Sequencing has revealed the causes of diseases, and nucleic-acid payloads, such as messenger RNA (mRNA), short-interfering RNA (siRNA), and DNA, alongside gene-editing tools have shown that it is possible to address their genetic drivers. Yet, the limitations of the technologies used to get the nucleic-acid payloads to their targets are preventing the development of safe, effective, and reproducible treatments. Entos Pharmaceuticals has developed a differentiated platform that could clear the bottleneck and help usher in a new era of genetic medicine.

Today, researchers use viral vectors and lipid nanoparticles (LNPs) to deliver genetic material. Both technologies hold great promise, but each has its own limitations. Vectors such as adeno-associated viruses trigger immune responses, preventing repeat dosing and causing troubling side effects, particularly when administered systemically. Viral vectors also have limited packaging capacity that prevents the delivery of many full-size genes.

Nonviral approaches such as LNPs have opened up a whole new approach to mRNA-based genetic medicines. While LNPs have performed exceptionally well in vaccines, such as shots to prevent COVID-19, their main challenge is their tendency to accumulate in the liver. This makes it particularly difficult to target the many diseases that occur outside the liver.

These inherent limitations of viral vectors and LNPs are holding the entire field of genetic medicine back. As Entos CEO John Lewis explained: "Without a safe, effective, and redosable extra-hepatic delivery platform, there will be few if any new curative drugs, because these amazing genetic tools we've developed can't get to the cells where they can affect that cure."

PLVs: solving the delivery problem

Entos has developed a delivery system to overcome the barrier to breakthrough genetic medicines. The Fusogenix proteolipid vehicle (PLV) platform combines the best features of LNPs and viral vectors to get RNA and DNA therapies to the targeted cells (Fig. 1).

PLVs are formulated using a unique fusion protein, discovered by Entos' co-founder Roy Duncan, professor at Dalhousie University, which is two orders of magnitude smaller than the other fusion proteins that viruses use. Entos developed a fully engineered version of the fusion protein, the activity of which replaces endosomal escape and provides a new way of delivering nucleic acids into cells.

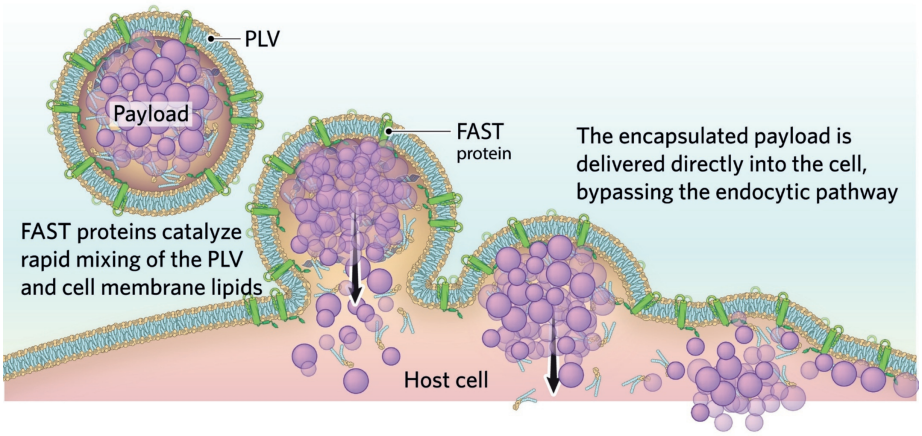

Fig. 1 | Nucleic acid drug delivery using the Fusogenix proteolipid vehicle (PLV) platform. The PLV platform can encapsulate any type of nucleic acid payload, target a broad range of host tissues, and is non-immunogenic and redosable.

The biotech formulates the protein in a lipid particle but, instead of entering and escaping from cells like LNPs, the vehicle fuses with the cellular membrane to deliver its payload without causing damage. Multiple preclinical studies show that PLVs address the limitations of existing delivery vehicles.

"We've created a platform that's considerably less toxic and better tolerated than LNPs and is completely non-liver targeted. We can administer PLVs systemically and they go everywhere in the body. We can hit all of the important gene-therapy targets—brain, lung, kidney, muscle, etc—to impact all the key genetic diseases that plague humanity," Lewis said.

Because PLVs are non-immunogenic, Entos can administer repeat doses without seeing reduced efficacy or causing toxicity. A scalable manufacturing process enables Entos to encapsulate large cargo, opening up opportunities to treat diseases such as cystic fibrosis that are beyond the packaging capacity of viral vectors, and combine DNA and RNA or multiple RNA molecules in a single PLV.

Partnering the platform

Entos has used PLVs to develop a fridge-stable, single-shot COVID-19 booster. The DNA PLV vaccine—the first of its kind—is cheaper to make than mRNA LNPs and could provide longer-lasting protection. While preparing to move the vaccine candidate into phase 3, Entos is also working to launch clinical trials for up to a dozen more internal programs in areas such as rare diseases over the next two years.

The internal programs are advancing in parallel to partnered projects. Entos finalized its largest deal in 2022, when it partnered with Eli Lilly to develop PLV candidates against multiple targets in the central and peripheral nervous systems. The deal is one of a set of external projects that includes a Bill & Melinda Gates Foundation infectious disease program and sister company Oisin Biotechnologies' work on age-related diseases.

Recognizing that the potential of the platform exceeds the bandwidth of any company, Entos is looking to form more partnerships. The biotech wants to team up with companies that have deep knowledge of targets and diseases, such as cystic fibrosis and muscular dystrophy, that could be treated with PLV-based genetic medicines.

Through the programs, Entos and its collaborators could validate the final piece of technology needed to unlock the potential of genetic medicines. The promise of years of work to identify genetic drivers of diseases and create the genetic-material payloads to address them is going unfulfilled because of the safety, biodistribution, and redosing limitations of delivery vehicles. In PLVs, biopharma may finally have the vehicle to fulfill that promise.

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