Vesigen Therapeutics
www.vesigen.com

ARMMs give a leg-up to novel biotherapeutics

By engineering naturally existing arrestin domain-containing protein 1 (ARRDC1)-mediated microvesicles (known as ARMMs), Vesigen Therapeutics' platform enables the effective delivery of novel biotherapeutics to specific tissues and cell types.

"The therapeutic potential of new gene-, RNA- and protein-based drugs is significantly constrained by delivery challenges," said Paulash Mohsen, CEO of Vesigen Therapeutics. "Despite tremendous advances in developing these types of therapies, the menu of effective delivery choices remains small."

While viral vectors and lipid nanoparticles are the main options to deliver gene therapies and therapeutic RNAs, they have important limitations, as Joseph Nabhan, CSO, experienced first-hand working in early-stage development programs before joining Vesigen. Nabhan explained, "these limitations extend across multiple dimensions, including biodistribution, loading capacity, immunogenicity, dose-limiting toxicity and manufacturing."

"Vesigen's drug delivery vehicles overcome these limitations; they can effectively reach cells and tissues that are otherwise inaccessible and deliver biologically active payloads without generating neutralizing antibodies that prevent re-dosing," Mohsen said. Another important advantage of Vesigen's approach is that manufacturing is easily scalable. "The production process involves readily available starting materials and standard unit operations used in the purification of other biologics," he added.

Vesigen Therapeutics is a biotechnology company based in Cambridge, Massachusetts, which launched in 2020 to develop and commercialize novel drug delivery technologies that originated from research led by Quan Lu at the Harvard T. H. Chan School of Public Health. The company employs approximately 40 people and is led by an interdisciplinary team with extensive experience in the discovery, development and commercialization of novel biotherapeutics.

Engineered ARMMs: a highly versatile delivery platform

When examining the mechanisms by which mammalian cells turn over membrane-associated proteins, Lu and colleagues identified a new intercellular-communication mechanism driven by ARRDC1 (arrestin domain containing protein 1) localized on the inner leaflet of the plasma membrane[1]. ARRDC1 triggers the formation of small (60 nm in diameter) vesicles that transport molecules between cells and can be engineered to efficiently deliver various protein and RNA payloads[2,3]. In preclinical studies at Vesigen, efficient delivery has been achieved in a range of tissues, including retinal, lung, nervous system, liver and spleen.

In addition to characterizing the biodistribution of ARMMs following different routes of administration, Vesigen has been exploring ways to re-direct the distribution of ARMMs to specific cell types that can currently be modified only ex vivo, such as T cells.

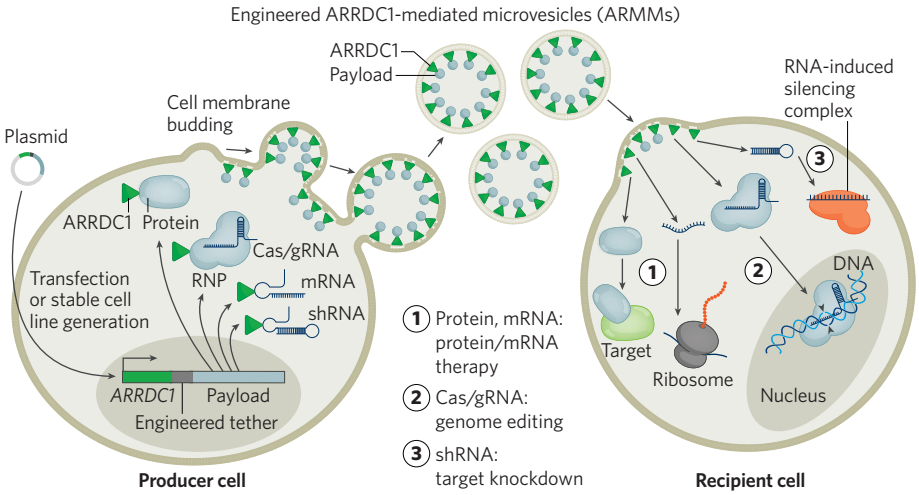

Fig. 1 | Schematic of how engineered ARMMs are produced to enable delivery of therapeutic payloads. Producer cells are modified to express ARRDC1, an engineered tether, and the payload(s) of interest. ARRDC1 is used as a handle that actively recruits payloads into the lumen of ARMMs, and as a potentiator of ARMMs biogenesis. When engineered ARMMs interact with recipient cells, they mediate functional delivery of the payload(s). ARMMs are modular non-viral vehicles that can deliver therapeutic Cas/gRNA RNP, protein, or RNA molecules to disease-affected cells. ARMMs, ARRDC1-mediated microvesicles; ARRDC1, arrestin domain-containing protein 1; Cas, clustered regularly interspaced short palindromic repeat (CRISPR)-associated endonuclease; gRNA, guide RNA; RNP, ribonucleoprotein; mRNA, messenger RNA; shRNA, short hairpin RNA.

"The potential to expand the number of cellular zip codes that ARMMs can reach drastically increases the number of indications we can tackle," said Nabhan.

One-step synthesis

Producing therapeutic ARMMs entails engineering producer cells to express the *ARRDC1* gene and the payload of interest. The therapeutic cargo is directly loaded into ARMMs, which can be collected and purified once they bud-off from producer cells (Fig. 1).

Vesigen has demonstrated that it can produce a high percentage of loaded vesicles each of which can load up to 15 base-editor complexes with guide RNA (gRNA) or 20 class 2 clustered regularly interspaced short palindromic repeat (CRISPR)-associated endonuclease 9 (Cas9)/gRNA complexes. The production system is robust and scalable to support the manufacturing necessary for clinical trials.

What's next?

Vesigen has generated and presented extensive data on the biodistribution and functional delivery of loaded ARMMs in cell-culture and rodent models and is now investigating translation into larger animals. "We have data showing remarkable translation of ARMMs biodistribution across mice, minipigs and non-human primates," said Mohsen.

The company's initial focus is to develop treatments for ocular, neurological, and immune-mediated inflammatory and fibrotic diseases. Given the modularity of ARMMs, they can potentially be applied to a wide range of indications either independently or in partnership with biopharmaceutical companies.

"Enabling effective delivery of gene-editing-, RNA- and protein-based therapeutics has the potential to dramatically increase the number of patients who may benefit from these next-generation medicines," Nabhan said. "We look forward to evaluating our engineered ARMMs in clinical studies and to realizing the full potential of this platform in human therapeutics."

1. Nabhan, J. F. et al. *Proc. Natl Acad. Sci. USA* **109**, 4146–4151 (2012). https://doi.org/10.1073/pnas.1200448109
2. Wang, Q. et al. *Nat. Commun.* **8**, 709 (2017). https://doi.org/10.1038/s41467-017-00767-2
3. Wang, Q. et al. *Nat. Commun.* **9**, 960 (2018). https://doi.org/10.1038/s41467-018-03390-x

CONTACT
Lorien Moore, VP Corporate Development and Business Operations
Vesigen Therapeutics
Cambridge, MA, USA
Tel: 1-857-299-6144
Email: lmoore@vesigen.com