Gene Delivery Vehicles

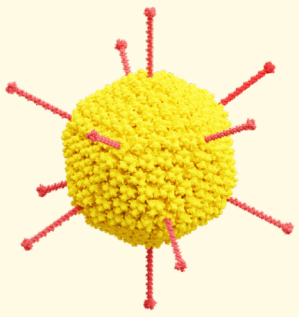
Building the perfect gene therapy requires matching the right delivery system, or vector, with a suitable genetic cargo enabling it to repair dysfunction at a target site. With nearly 10,000 monogenic diseases, clinicians and scientists looking to cure diseases in specific cell types must navigate tradeoffs between a delivery vehicle's cargo capacity, tissue targets, immune responses, and cost.

PDB: 7KP3

Adeno-Associated Virus (AAV)

AAV vectors are small, replication-deficient viruses that persist in non-dividing cells for years, making them ideal for long-term gene expression. AAVs are used in multiple FDA-approved therapeutics, including Luxturna, Zolgensma, and Hemgenix. Many are working to make AAVs that more specifically target desired cells in the brain or muscles. The major limitation of AAVs is their packaging capacity of 4.7 kb, which restricts delivery of larger therapeutic genes or CRISPR systems. About 80% of people also have pre-existing neutralizing antibodies, meaning they have a high risk of unwanted immune responses that would render a gene therapy ineffective or cause side effects including severe illness.

Genetic payload size: up to 4.7 kb — ssDNA

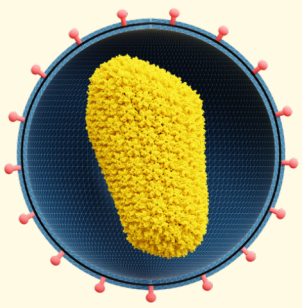


PDB: 1QIU & 6CGV

Adenovirus

Adenoviral vectors have large packaging capacities (up to 36 kb) and are widely used to develop vaccines, including for COVID-19 and Ebola, and emerging cancer therapies. Their large cargo capacity makes them suitable for delivering complex genetic payloads that exceed AAV limits. However, they trigger strong immune responses that can be life-threatening. Up to 70% of adults carry neutralizing antibodies against common adenovirus serotypes. Adenovirus expression is also transient, meaning the recipient needs to be repeatedly dosed to maintain long-term therapeutic benefits.

Genetic payload size: up to 36 kb — dsDNA



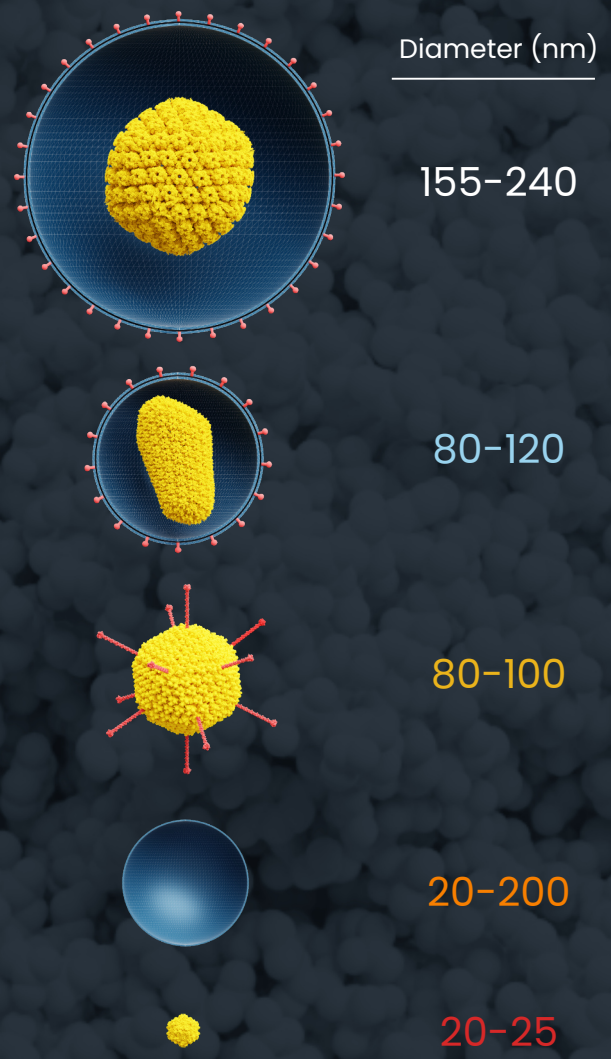
PDB: 3J3Y

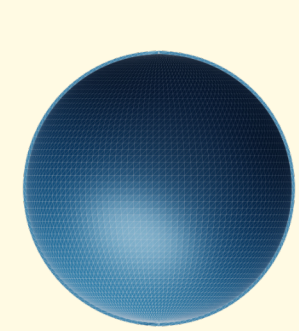
Lentivirus

Lentiviral vectors integrate permanently into the host genome, thus enabling stable, long-term gene expression in both dividing and non-dividing cells. Capable of packaging up to 10 kb reliably, they are used in multiple FDA-approved ex vivo therapies, including CAR-T cell treatments (Kymriah, Yescarta) and genetic disease therapies (Zynteglo, Libmeldy). However, because lentiviruses integrate into the genome, drug developers worry they could unintentionally activate oncogenes and cause cancer. For this reason, they are mainly used in ex vivo applications; because edited cells can be screened for genetic defects before being reinfused back into the body.

Genetic payload size: up to 9.7 kb — ssRNA

Scale of Delivery Vehicles

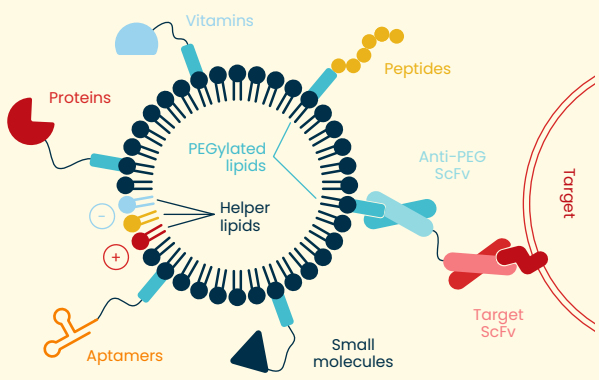


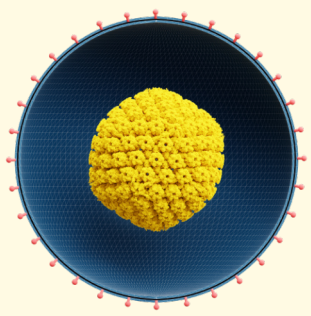


Lipid Nanoparticles

Lipid nanoparticles are cheap to make and excel at delivering mRNA molecules, rapidly coaxing cells to make proteins. Some formulations can be redosed safely, with minimal immune responses, and are theoretically not gated by any size restrictions, though commercial LNP services generally stop at 10 kb. They are widely used for COVID-19 vaccines and, more recently, for therapeutics targeting the liver. Scientists are making advances in LNP engineering that help them deliver to organs beyond the liver by modifying lipid composition and decorating the surface with molecules such as peptides, proteins, apatamers, and antibodies, but this has yet to be tested in humans. Until that happens, the main limitations include difficulty targeting tissues outside the liver-lung-muscle triad and transient expression requiring repeated dosing.

Genetic payload size: Variable — mRNA and more





PDB: 6CGR

Herpes Simplex Virus

Herpes simplex virus has a large cargo capacity (about 152 kb) and natural neurotropism, making them well-suited for brain and nervous system applications. T-VEC's FDA approval for melanoma demonstrates their clinical viability, particularly as oncolytic therapies that selectively kill cancer cells while sparing normal tissue. HSV naturally lies dormant in neurons after infection in humans, which, when applied to a gene therapy, enables persistent gene expression in these cells. However, more than 60% of people have pre-existing immunity to the herpes virus, meaning the virus can induce cytotoxicity that compromises long-term gene expression.

Genetic payload size: up to 152 kb — dsDNA

Credits

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For a full list of citations, see our accompanying article at press.asimov/articles/gene-delivery-guide or on our Substack at asimov.press/p/gene-delivery-guide

Additional illustration citations:
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