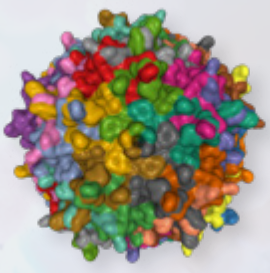
Viral Vector Engineering

Viral vectors are viruses engineered to deliver therapeutic genes into cells. This infographic examines viral vector types, their strengths and weaknesses, plus provides applications and examples of this paradigm-changing gene delivery technology.

Viral and Non-Viral Vectors

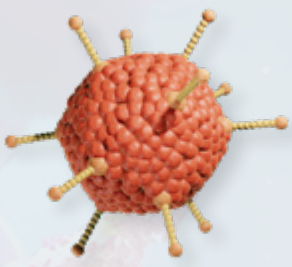
Non-viral gene delivery vectors include liposomes and nanoparticles capable of carrying genes into cells. Metallic, polymeric, composite, or carbon nanotube nanoparticle vectors carry large genetic payloads, have low toxicity, and are inexpensive but transfer genes inefficiently, have poor specificity, and their gene constructs are short-lived. Where nanoparticle vectors are limited by their physical dimensions and material composition, viral vectors may be designed to target specific cells or tissues, or for specific conditions.

Four viruses make up the lion's share of viral vectors:[1]



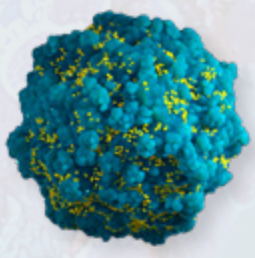
Adeno-associated viral (AAV) vectors

deliver smallish DNA packages, are non-integrating (daughter cells will not carry the gene), and typically target the liver, nervous system, eyes, and skeletal cells. AAVs often persist in patients, of whom up to 70% are treatment-ineligible due to anti-AAV responses to previous exposure to infectious AAVs.



Adenoviral vectors

resemble AAVs in most respects but carry larger genetic payloads and may be engineered to elicit milder immune responses. Like AAVs, adenovirus vectors are non-integrative.



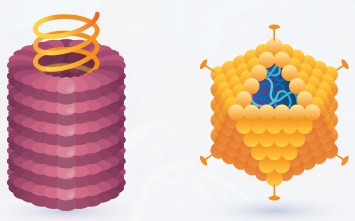
Lentiviral and retroviral vectors

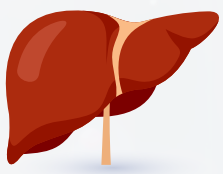
carry larger payloads of RNA, which cells convert to DNA and integrate into their genomes. To exploit this mechanism lenti/retroviral vectors target dividing cells such as immune or stem cells which are typically harvested, treated *ex vivo*, expanded, and re-introduced into the patient.

Why Engineer Viral Vectors?

Quality improvements through formulation: Viral vector formulations are designed to preserve a vector's activity, stability, and overall quality through optimizing pH, osmolality, the addition or choice of salts, surfactants, free radical scavengers, or through chemical modification of the capsid.

Overcoming immune responses, greater overall safety: Despite their inherent safety, AAV-based therapies are limited by neutralizing antibodies.[2] To avoid this, AAV vectors have been designed with modified protein capsids. Engineered AAVs have the added benefits of avoiding disfavored immune responses, overcoming the payload size limit, and the potential to deliver two or more genes simultaneously.



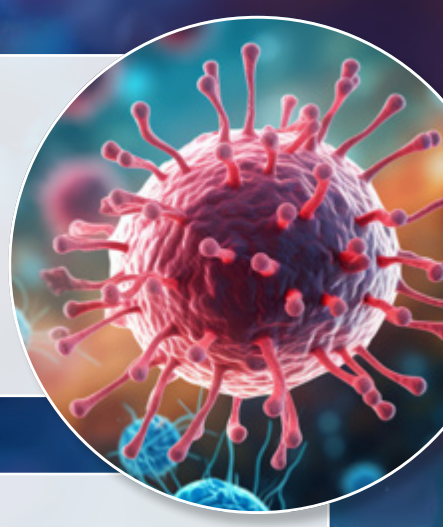


Improving tissue specificity: AAV vectors accumulate in the liver,[3] from where they may cause localized or systemic toxicity and off-target effects. These are minimized through control of AAV capsid tissue/cell tropism,[4] the use of tissue-specific promotors,[5] or by changing the administration route.[6]

Gene transfer efficiency: Getting genes into cells is the end result of a long sequence of events, all requiring optimization. Choice of viral vector is the first decision, as some vectors transfect certain cell types more efficiently than others. Maintaining the gene's stability is another factor. Controlling tropism (a factor in tissue specificity) may occur at the structural level by introducing target-specific carbohydrate or other residues onto vectors. A greater understanding of secondary binding between vector and cell could facilitate gene transfer and transduction.[7]

AI and Vector Design

Researchers are exploring artificial intelligence (AI) to improve the safety and effectiveness of both viral and nonviral vectors.[8] A University of Toronto group, for example, used AI to reduce the immunogenicity of an adenovirus vector.[9] Once a delivery vector is selected, AI can also assist in clinical trial design through a "totality of data approach" to support dose, end point, and patient selection.[10]



References

1 https://patienteducation.asgct.org/gene-therapy-101/vectors-101
2 https://pubs.acs.org/doi/abs/10.1021/acsnano.0c03850
3 https://www.nature.com/articles/s42003-023-04851-w
4 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4993104/
5 https://link.springer.com/article/10.1007/s40259-017-0234-5
6 https://www.frontiersin.org/articles/10.3389/fnmol.2022.988914/full#:~:text=For%20example%2C%20in%20some%20disorders,injections%20with%20retrograde%20and%20anterograde
7 https://www.sciencedirect.com/science/article/pii/S0753332220304686
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