Viral vectors in Parkinson's disease treatment

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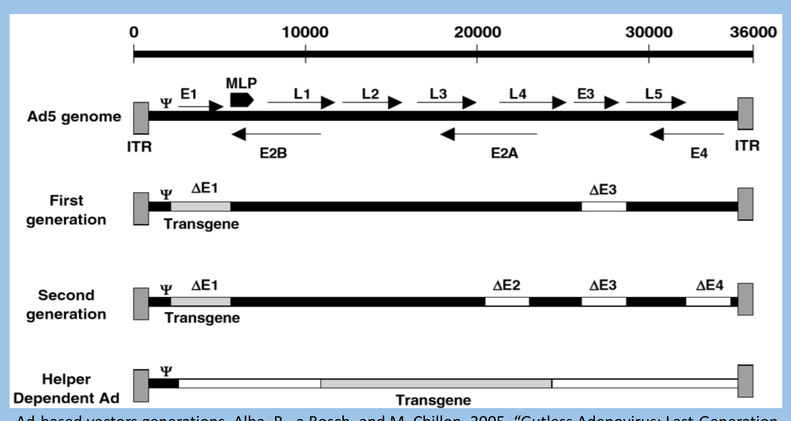
INTRODUCTION

Parkinson's disease is a neurodegenerative disorder, which is characterized by the loss of dopaminergic neurons in substantia nigra. Also, it is observed the presence of cytoplasmic inclusions (Lewy's body or LB), made of α-synuclein, but also Lewy's neurites (LN) formed by α-synuclein and ubiquitin. Despite environment play an important role in Parkinson development, there are also some genetic factors that can imply Parkinson's disease. These genetic features are assembled in two groups, α-synuclein and recessive genes (parkin, DJ-1 and PINK1). In this context, gene therapy has become in one of the most interesting fields due to the possibility to transfer corrected genes in affected cells or prevent cell death and stimulate dopaminergic neuronal proliferation. In this context, high efficiency and security of viral vectors make these the main alternative for delivery.

VIRAL VECTORS

Adenoviral vectors [1]

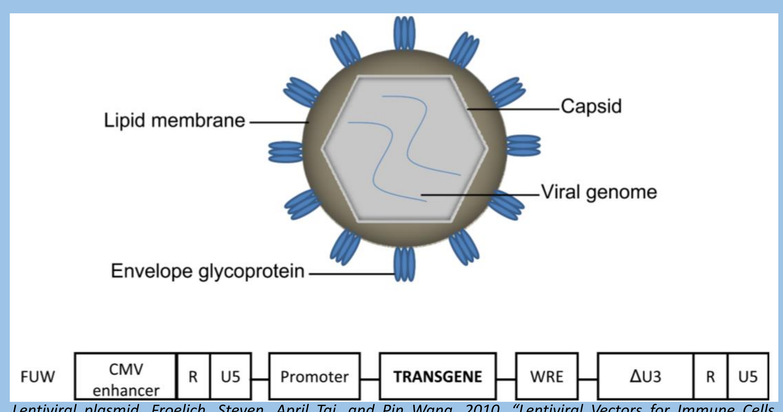
- ✓ Non-enveloped, icosahedral, DNA
- ✓ Structural proteins: hexon, penton and fibre, IIIa, VI, VIII and IX (small proportion)
- ✓ 4,5-30 kb DNA packaging capacity
- ✓ Immunogenic
- ✓ Long-term episomal expression
- ✓ Different generations: less viral content on genome
- ✓ Endosomal trafficking



Ad-based vectors generations. Alba, R., a Bosch, and M. Chillon. 2005. "Gutless Adenovirus: Last-Generation Adenovirus for Gene Therapy." Gene therapy 12 Suppl 1:S18–27.

Lentiviral vectors [2]

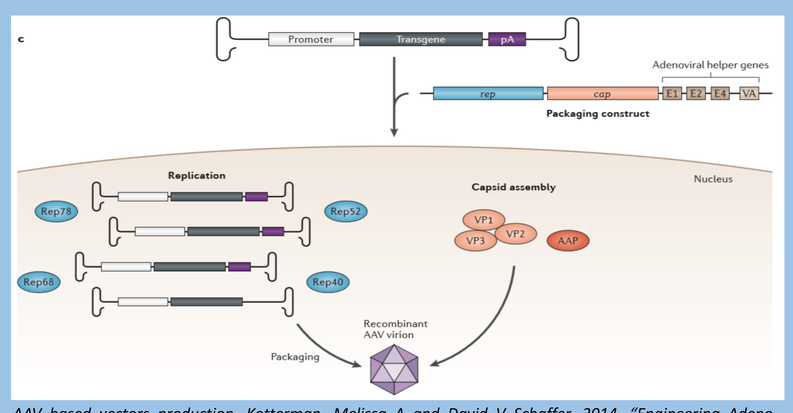
- ✓ Enveloped, spherical, RNA
- ✓ Structural proteins: gag, pol, and env
- ✓ Other proteins: rev, tat (regulatory), vpu, vpr, vif and nef (accessory).
- ✓ 7-12 kb DNA packaging capacity
- ✓ Long-term integrated expression
- ✓ Different generations: LTR and U3 modified, viral genes elimination
- ✓ RNA released on cytoplasm



Lentiviral plasmid. Froelich, Steven, April Tai, and Pin Wang. 2010. "Lentiviral Vectors for Immune Cells Targeting." 32(2):208–18.

Adenoassociated vectors [3]

- ✓ Non-enveloped, icosahedral, DNA
- ✓ Structural proteins: VP1, VP2 and VP3
- ✓ 4,7 kb DNA packaging capacity
- ✓ Multiple serotypes (AAV1-12) and tropism
- ✓ Low immunogenicity and non-pathogenic
- ✓ Long-term episomal expression
- ✓ Endosomal trafficking
- ✓ Vector generation: rep and cap substitution by transgene



AAV.-based vectors production. Kotterman, Melissa A and David V Schaffer. 2014. "Engineering Adeno-Associated Viruses for Clinical Gene Therapy." Nature reviews. Genetics 15(7):445–51.

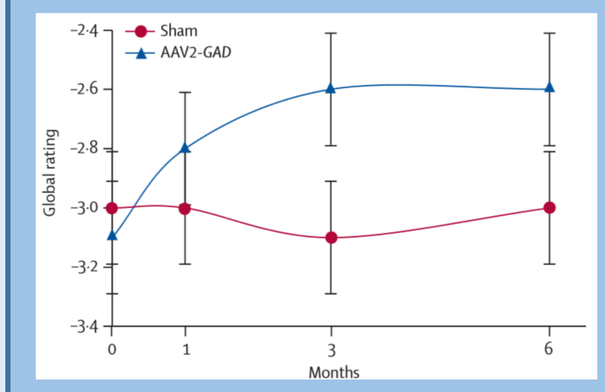
ACTUAL APPROACHES

Most of the studied genes code for neurotrophic factors that either promote neuroprotection or induce neuron growth, but also genes that code for different enzymes involved in dopamine synthesis. AAV-based vectors, which are non-pathogenic and non-immunogenic, are the most used vectors, also due to high neuron tropism.

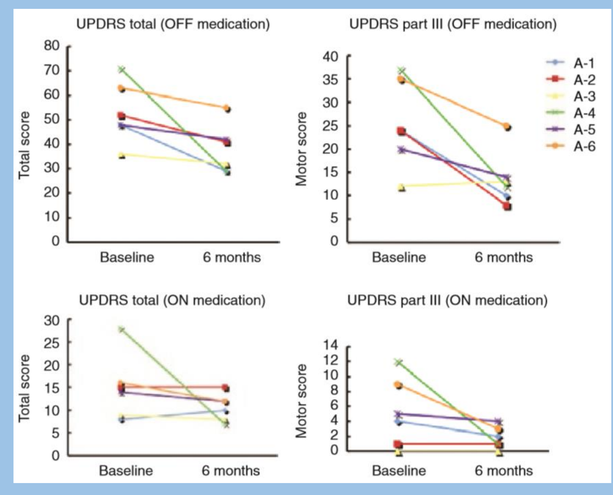
THERAPY	VECTOR	PHASE	ADMINISTRATION	DA SURVIVAL	UPDR IMPROVEMENT
GAD [4]	AAV2	Phase 2	Bilaterally injected into the STN	-	8,1 points
AADC [5]	AAV2	Phase 1	Bilaterally injected into the putamen	56%	30-46%
AADC/TH/GCH [6]	AAV and LV	Preclinical	Injected into the striatum	-	60%
NRTN [7]	AAV2	Phase 2	Bilaterally injection into the putamen	62%	88%
GDNF [8]	Ad, LV and AAV2	Preclinical	Injected into the striatum	48,70%	-
VEGF [9]	AAV2	Preclinical	Injected into the striatum	-	-
NURR1/FOXA2 [10]	AAV2 and LV	Preclinical	Injected into the peritoneum	69%	-

Comparative resume of different therapies trails developed

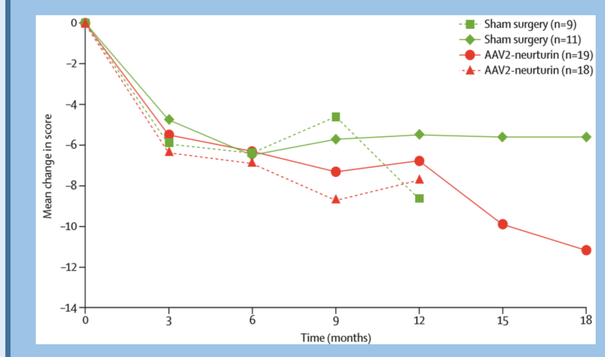
- ✓ Every therapy showed an evident improvement in Parkinson's symptoms and neuronal characteristics.
- ✓ Any problem derived from viral vectors was observed.
- ✓ AAV2 are the most employed vectors.



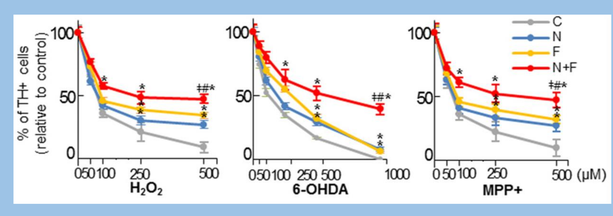
Global rating of parkinsonism (a question from the brief parkinsonism rating scale) showed a significant difference between groups on a phase II AAV2-GAD trial. LeWitt, Peter a. et al. 2011. "AAV2-GAD Gene Therapy for Advanced Parkinson's Disease: A Double-Blind, Sham-Surgery Controlled, Randomised Trial." The Lancet Neurology 10(4):309–19.



Changes in UPDRS scores in a phase 1 clinical trial of AAV2-AADC. Absolute changes in scores from baseline to 6 months for individual patients. OFF, off-medication state; ON, on-medication state; UPDRS, Unified Parkinson's Disease Rating Scale. Muramatsu, Shin-Ichi et al. 2002. "Recombinant Adeno-Associated Viral Vectors Bring Gene Therapy for Parkinson's Disease Closer to Reality." Journal of neurology 249 Suppl :II36–I40



Mean change from baseline in the subgroup of patients of a phase 2 clinical trial of AAV2-NRTN therapy. Marks, William J. et al. 2010. "Gene Delivery of AAV2-Neurturin for Parkinson's Disease: A Double-Blind, Randomised, Controlled Trial." Lancet neurology 9(12):1164–72.



mDA neurons in the cultures transduced with Nurr1 and/or Foxa2. The mDA neuron–glia cultures were transduced with lentiviruses expressing Nurr1 (N), Foxa2 (F), Nurr1 + Foxa2 (NF), or control (C) and treated with the toxin for 8 h. Oh, Sang-min et al. 2015. "Combined Nurr 1 and Foxa 2 Roles in the Therapy of Parkinson's Disease." 1–17.

CONCLUSION

1. Prevention of neurodegeneration
2. Improvement of symptoms: tremor and dyskinesia
3. Higher production of dopamine
4. High safety of vectors: AAVs as the best vectors
5. Modest results
6. Possible upgrades: different or new vectors or other administration via
7. Potential therapy

REFERENCES

[1] Alba, R., a Bosch, and M. Chillon. 2005. "Gutless Adenovirus: Last-Generation Adenovirus for Gene Therapy." Gene therapy 12 Suppl 1:S18–27. [2] *Froelich, Steven, April Tai, and Pin Wang. 2010. "Lentiviral Vectors for Immune Cells Targeting." 32(2):208–18.* [3] *Kotterman, Melissa A and David V Schaffer. 2014. "Engineering Adeno-Associated Viruses for Clinical Gene Therapy." Nature reviews. Genetics 15(7):445–51.* [4] LeWitt, Peter a. et al. 2011. "AAV2-GAD Gene Therapy for Advanced Parkinson's Disease: A Double-Blind, Sham-Surgery Controlled, Randomised Trial." The Lancet Neurology 10(4):309–19. [5] Muramatsu, Shin-Ichi et al. 2002. "Recombinant Adeno-Associated Viral Vectors Bring Gene Therapy for Parkinson's Disease Closer to Reality." Journal of neurology 249 Suppl :II36–I40. [6] Jarraya, Béchir et al. 2009. "Dopamine Gene Therapy for Parkinson's Disease in a Nonhuman Primate without Associated Dyskinesia." Science translational medicine 1(2):2ra4 [7] Marks, William J. et al. 2010. "Gene Delivery of AAV2-Neurturin for Parkinson's Disease: A Double-Blind, Randomised, Controlled Trial." Lancet neurology 9(12):1164–72. [8] Björklund, a. et al. 2000. "Towards a Neuroprotective Gene Therapy for Parkinson's Disease: Use of Adenovirus, AAV and Lentivirus Vectors for Gene Transfer of GDNF to the Nigrostriatal System in the Rat Parkinson Model." Brain Research 886(1-2):82–98. [9] Tian, You-yong et al. 2007. "Favorable Effects of VEGF Gene Transfer on a Rat Model of Parkinson Disease Using Adeno-Associated Viral Vectors." Neuroscience letters 421(3):239–44. [10] Oh, Sang-min et al. 2015. "Combined Nurr 1 and Foxa 2 Roles in the Therapy of Parkinson's Disease." 1–17.