Fetal Gene Therapy

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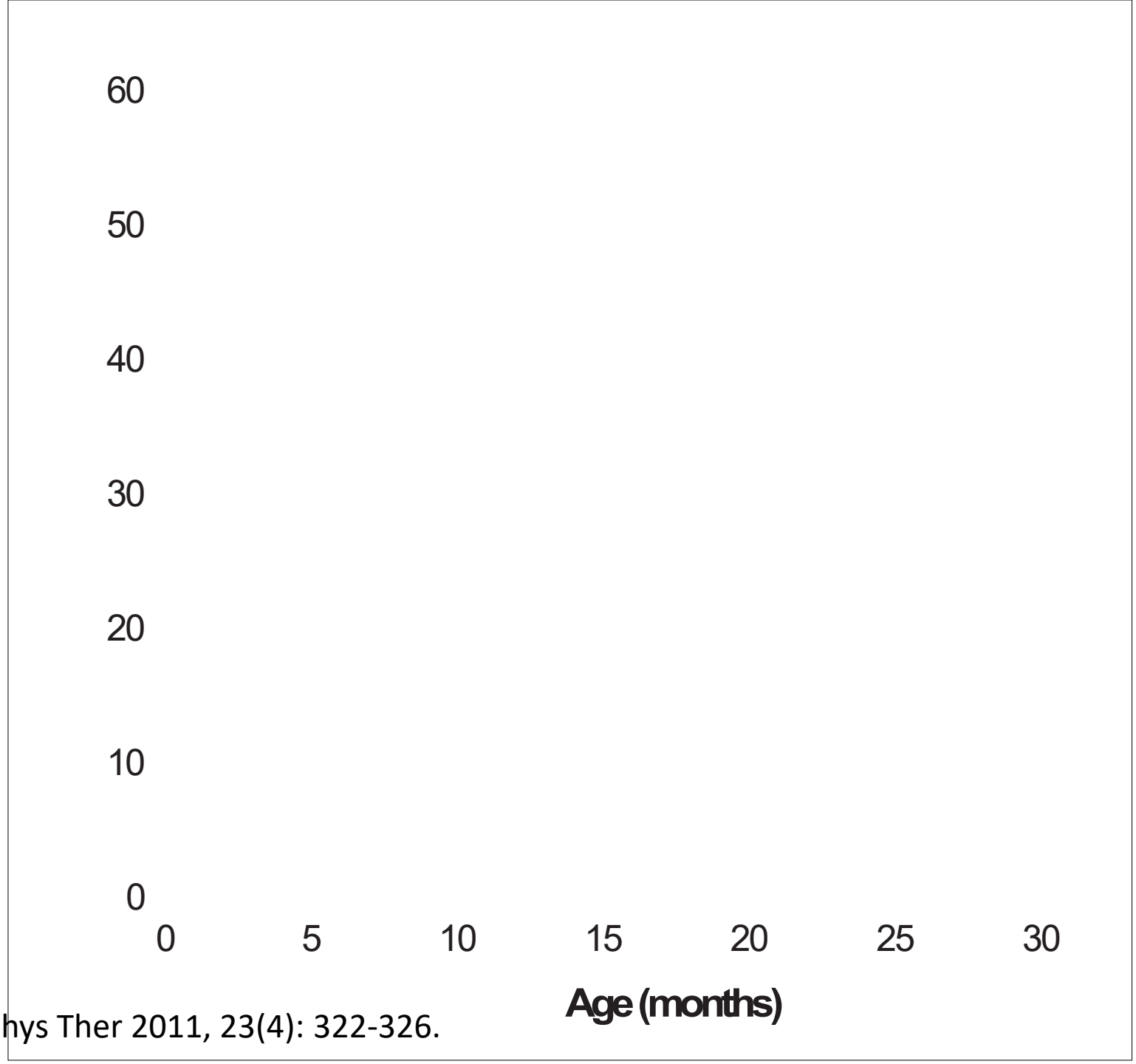
- Gene therapy works
- Why fetal gene therapy?
- Immunological benefits
- Therapeutic benefits
- Challenges & criteria

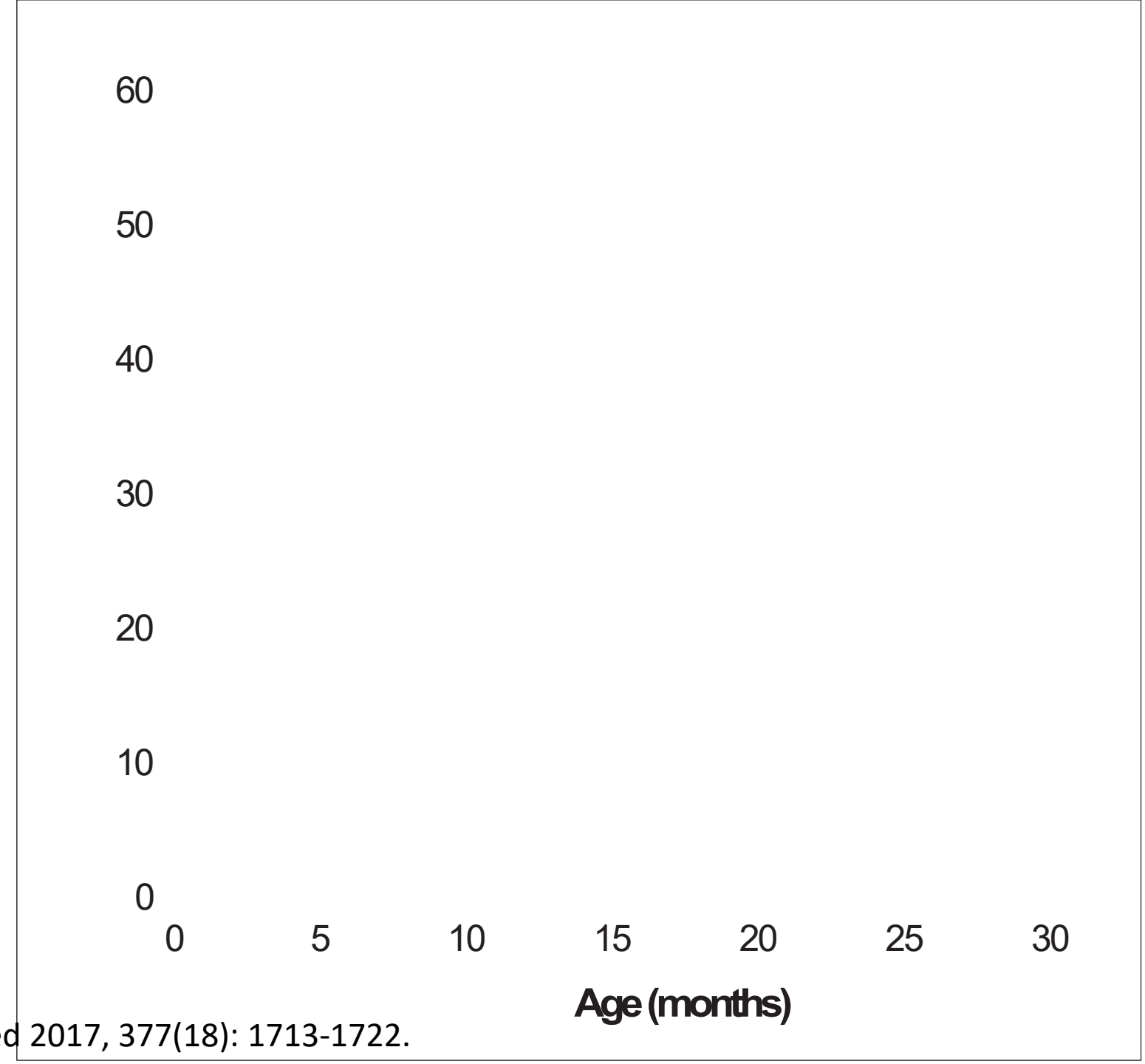

Amanda Cardoze

	Type I Spinal Muscular Atrophy
SMN2 copy number	Two
Onset	Before 6 months
Incidence per live births	Approximately 60%
Developmental milestones	Will never be able to sit without support Difficulty breathing and swallowing Can't crawl/will never walk
Survival	<10% event-free* by two years of age

*Event = Death or ≥16hr/day ventilation continuously for ≥2 wks, in the absence of an acute reversible illness



Glanzman AM, Pediatr Phys Ther 2011, 23(4): 322-326.



Mendell JR, N Engl J Med 2017, 377(18): 1713-1722.

Zolgensma

Luxterna

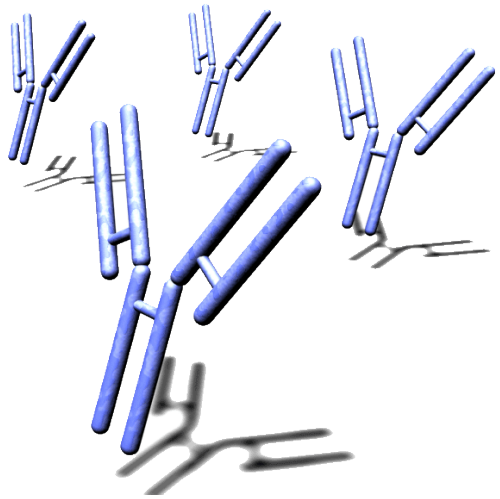
Gene Therapy Market Report Scope

Report Attribute	Details
Market size value in 2021	USD 3.42 billion
Revenue forecast in 2028	USD 10.0 billion
Growth Rate	CAGR of 20.4% from 2021 to 2028
Base year for estimation	2020
Historical data	2017 - 2019
Forecast period	2021 - 2028
Quantitative units	Revenue in USD million/billion and CAGR from 2021 to 2028
Report coverage	Revenue forecast, company ranking, competitive landscape, growth factors, and trends
Segments covered	Indication, vector type, region
Regional scope	North America; Europe; Asia Pacific; Rest of the World

https://www.grandviewresearch.com/industry-analysis/gene-therapy-market

Prevent or treat diseases where postnatal therapy is inadequate

Immunity

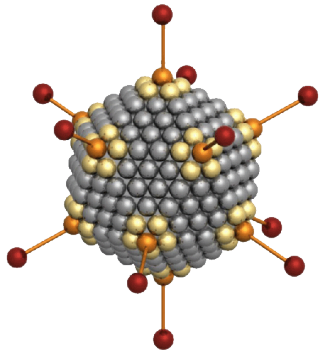


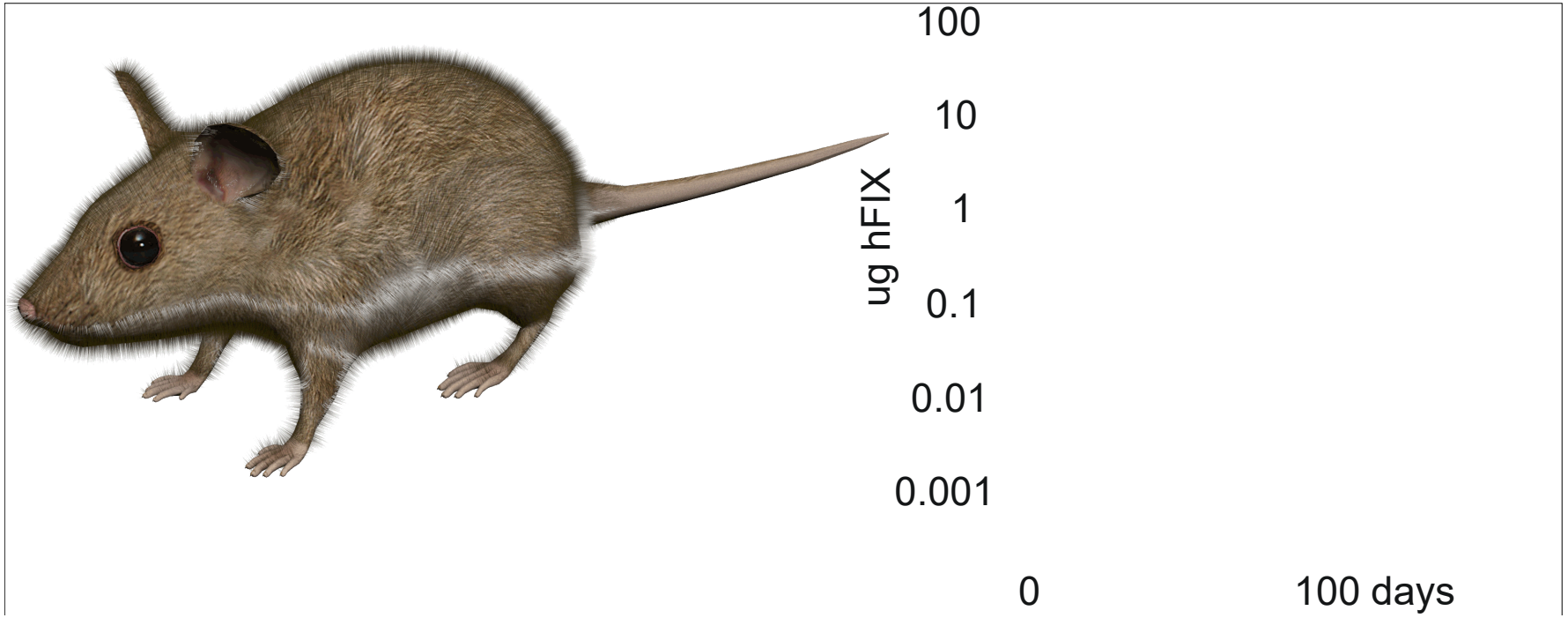
Efficiency

Immunity

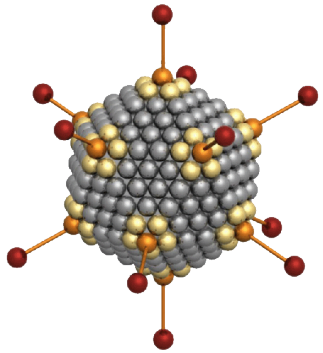
Immune tolerance to transgenic protein

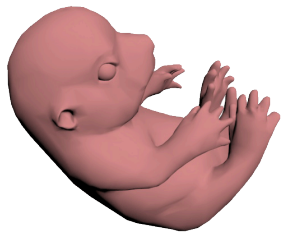
Avoidance of anti-capsid immune response





Waddington SN, et al. *Blood.* 2003;101:1359-1366.





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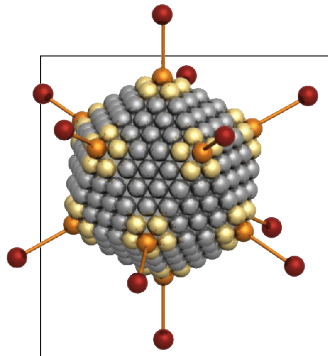

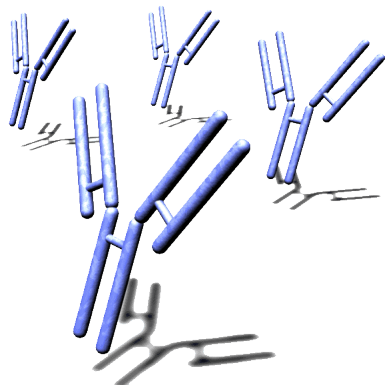

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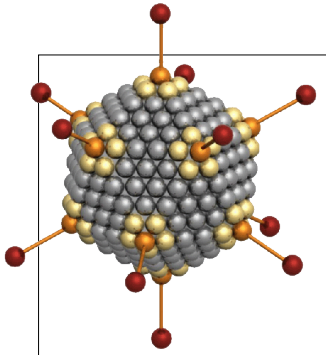

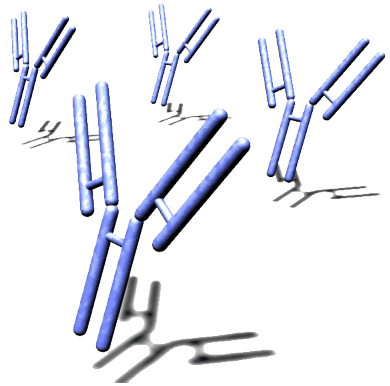

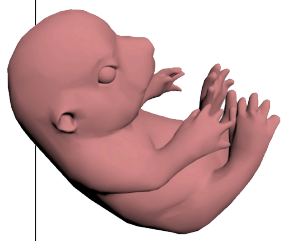

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Immunity

Immune tolerance to transgenic protein

Avoidance of anti-capsid immune response

Pre-existing immunity

Gene Therapy (2011), 1–7

www.nature.com/gt

ORIGINAL ARTICLE

Neutralizing antibodies against adeno-associated virus examined prospectively in pediatric patients with hemophilia

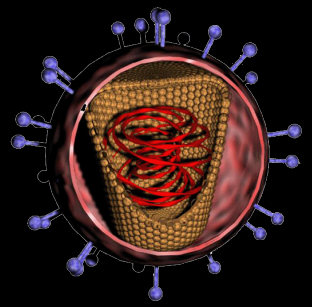
C Li[1,2], N Narkbunnam[1,3], RJ Samulski[1,4], A Asokan[1,5], G Hu[1], LJ Jacobson[6], MJ Manco-Johnson[6], PE Monahan[1,2] and The Joint Outcome Study Investigators[7]

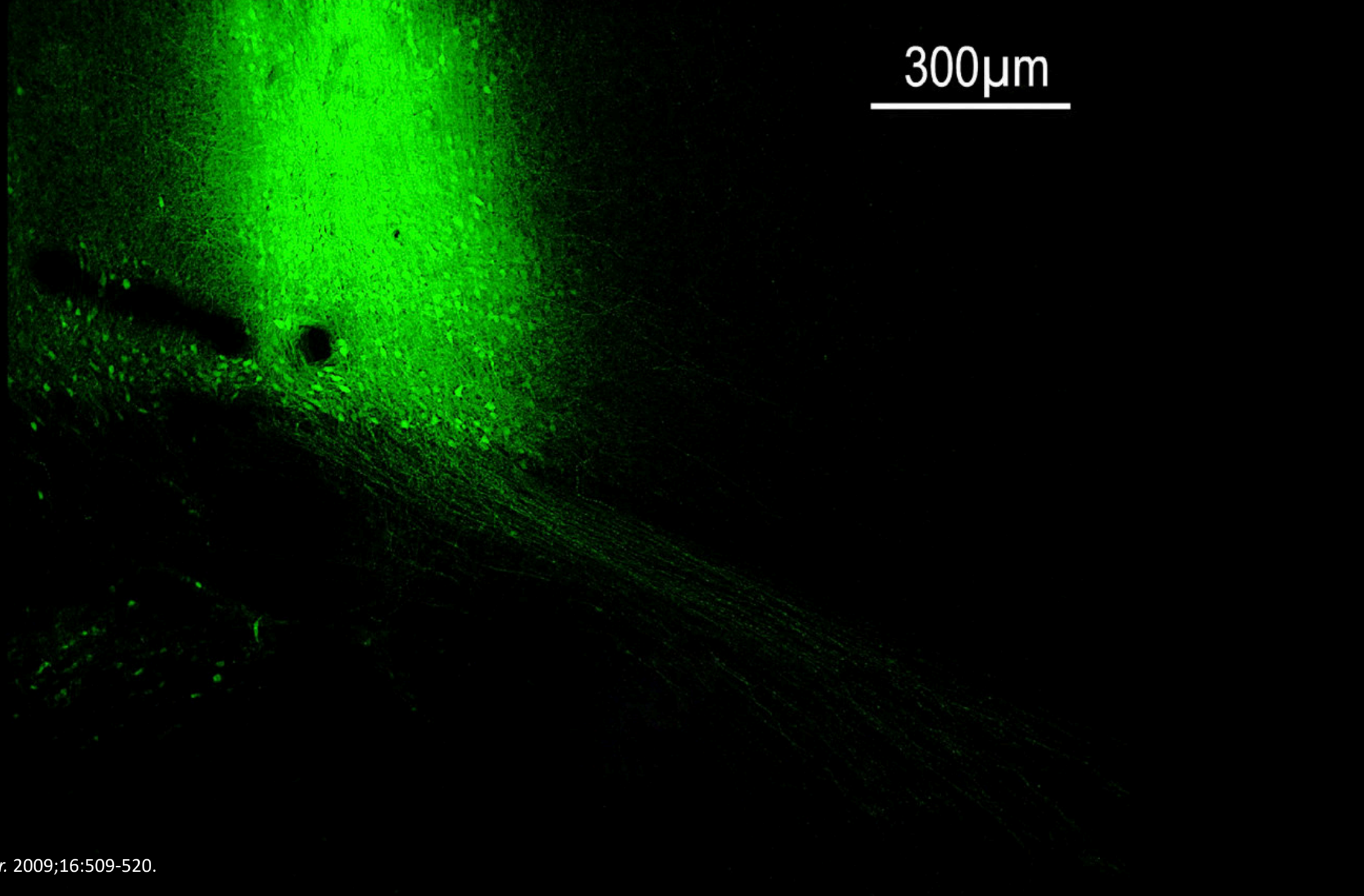
Recombinant adeno-associated virus (rAAV) is a promising gene delivery vector and has recently been used in patients with hemophilia. One limitation of AAV application is that most humans have experienced wild-type AAV serotype 2 exposure, which frequently generates neutralizing antibodies (NAbs) that may inhibit rAAV2 vector transduction. Employing alternative serotypes of rAAV vectors may circumvent this problem. We investigated the development of NAbs in early childhood by examining sera gathered prospectively from 62 children with hemophilia A, participating in a multi-institutional hemophilia clinical trial (the Joint Outcome Study). Clinical applications in hemophilia therapy have been suggested for serotypes AAV2, AAV5 and AAV8, therefore NAbs against these serotypes were serially assayed over a median follow-up of 4 years. NAbs prevalence increased during early childhood for all serotypes. NAbs against AAV2 (43.5%) were observed more frequently and at higher titers compared with both AAV5 (25.8%) and AAV8 (22.6%). NAbs against AAV5 or AAV8 were rarely observed in the absence of co-prevalent and higher titer AAV2 NAbs, suggesting that NAbs to AAV5 and AAV8 were detected following AAV2 exposure due to partial cross-reactivity of AAV2-directed NAbs. The results may guide rational design of clinical trials using alternative AAV serotypes and suggest that younger patients who are given AAV gene therapy will benefit from the lower prevalence of NAbs.
Gene Therapy advance online publication, 23 June 2011; doi:10.1038/gt.2011.90

Efficiency

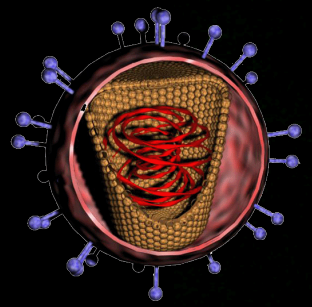
Higher efficiency

Preventing irreversible pathological changes





Rahim AA, et al. *Gene Ther.* 2009;16:509-520.



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Efficiency

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Preventing irreversible pathological changes

Challenges & criteria

- Ability to diagnose early
- Defined natural history
- Good biomarkers
- Sufficient patient numbers
- Centers with sufficient expertise
- Parental acceptance
- Clear benefit of fetal vs. postnatal gene therapy

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