

Suprachoroidal delivery for ocular gene therapy: nonclinical experiments evaluating non-viral DNA nanoparticles.

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None relevant to this presentation

DNA nanoparticles offer the potential for safe, efficacious, and repeat dosing of ocular gene therapy

Potential advantages:

- Unlike AAV (payload capacity of 5 kb), can transfer large genes (up to ~20 kb)
- Safety: Non-immunogenic, without viral capsid proteins or pre-existing immunity.
 - Potential for repeat and greater dosing
- Efficacy: in numerous ocular animal model, higher doses may be used to enhance transfection
- Manufacturing, Simpler than viral-based gene therapy

Potential disadvantages:

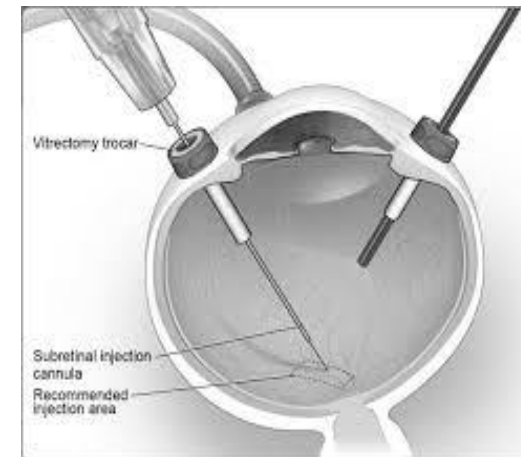
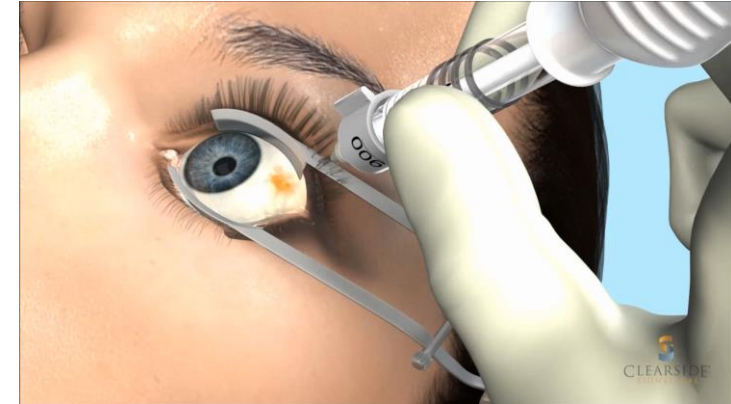
- Durability: May not represent one time therapy

DNA nanoparticle Gene Therapy: Well established literature



Suprachoroidal (SC) injection offers the potential for safe, targeted, and efficient ocular gene therapy

- **Targeted treatment** of posterior tissues possible via SC injection
 - Spread of injectate flows circumferentially and posteriorly
- **Safety**
 - Avoids the risks of sub-retinal surgery
 - Does not require detachment of the photoreceptors from the RPEs, without associated risk of iatrogenic injection to already compromised disordered retina
 - SC injection procedure training is minimal
- **Access to care**
 - Does not require specialized gene therapy surgery treatment centers
 - In-office SC injection procedure is less expensive than surgical procedures
 - Procedure time is significantly less than standard sub-retinal procedure



Suprachoroidal Injection of DNPs in Non-Human Primates and Rabbits

Study Objective

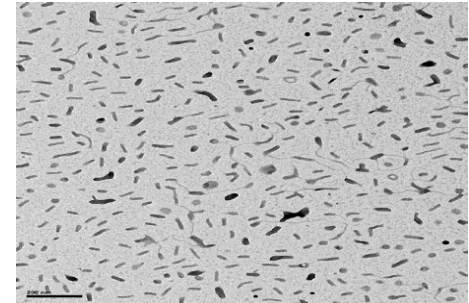
- Evaluate the safety, tolerability, and retinal cell transfection following SC injection of DNPs

Design

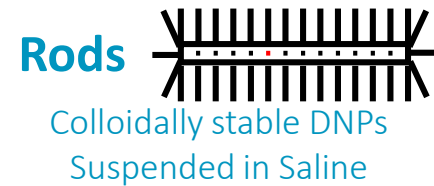
- Ophthalmic examinations at Day 0, 1, and 7
 - Surface morphology, ocular inflammation, direct and indirect ophthalmoscopy, IOP, ERG
- Eyes were enucleated at Day 7 and 21
 - Choroid and retina separated and processed for evaluation of luciferase activity



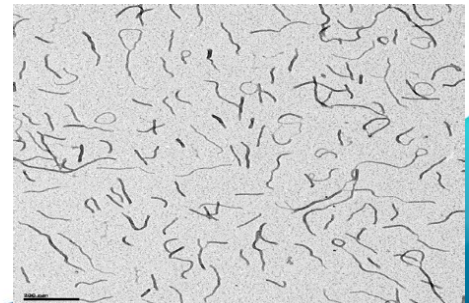
Ellipsoids
Colloidally stable DNPs
Suspended in Saline










8-10 nm in diameter



Rods
Colloidally stable DNPs
Suspended in Saline

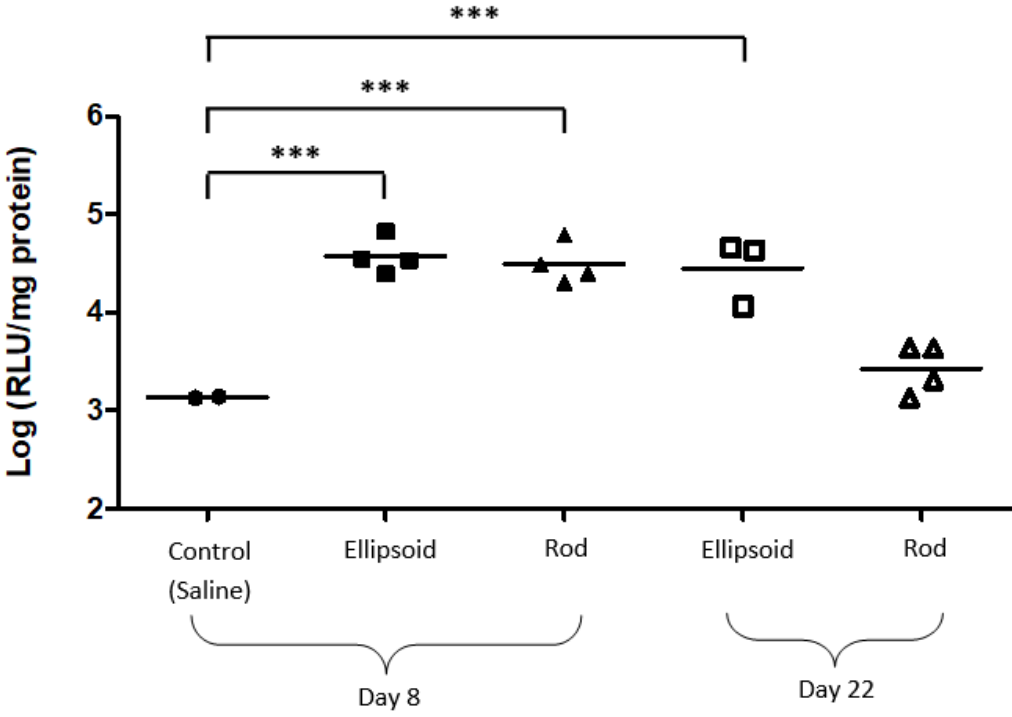


Species	Group (n=4)	Test article	Route of Administration	Volume
	1	Vehicle	SC Injection	100 μ L
	2	 Ellipsoid DNPs Luciferase	SC Injection	100 μ L
	3	 Rod DNPs Luciferase	SC Injection	100 μ L
	1	Vehicle	SC Injection	100 μ L
	2	 Ellipsoid DNPs Luciferase	SC Injection	100 μ L
	3	 Rod DNPs Luciferase	SC Injection	100 μ L
	4	 Rod DNPs Luciferase	Sub-retinal injection	50 μ L

NHP: DNA Nanoparticles Transfect RPE + Choroid and Retina

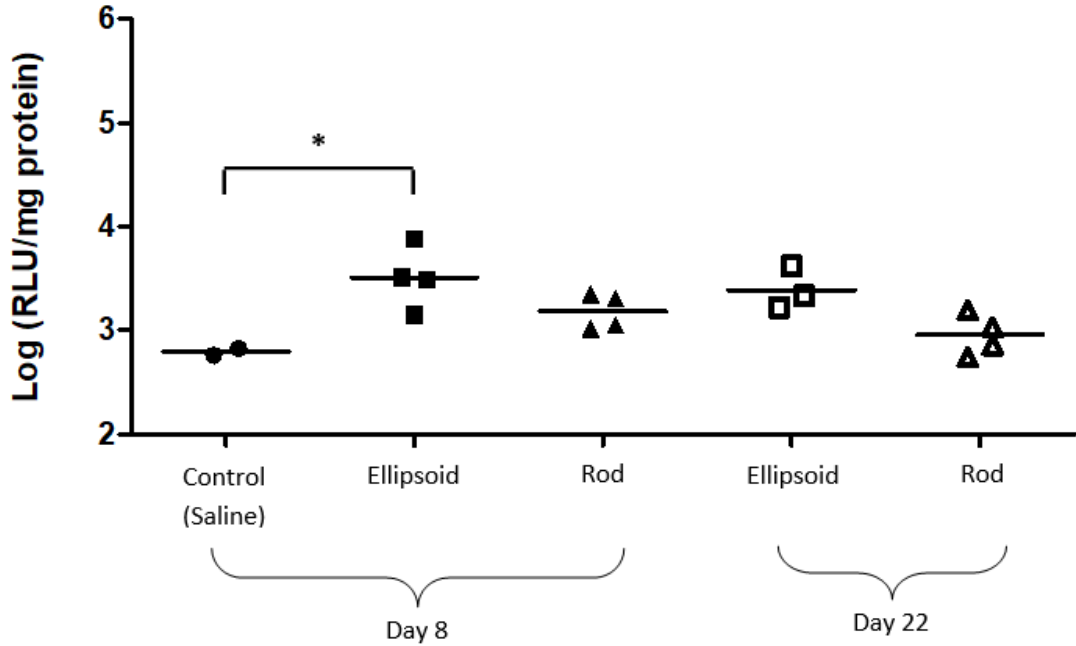


RPE-CHOROID



1-way ANOVA, $p < 0.0001$.
Bonferroni's multiple comparison test: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

RETINA

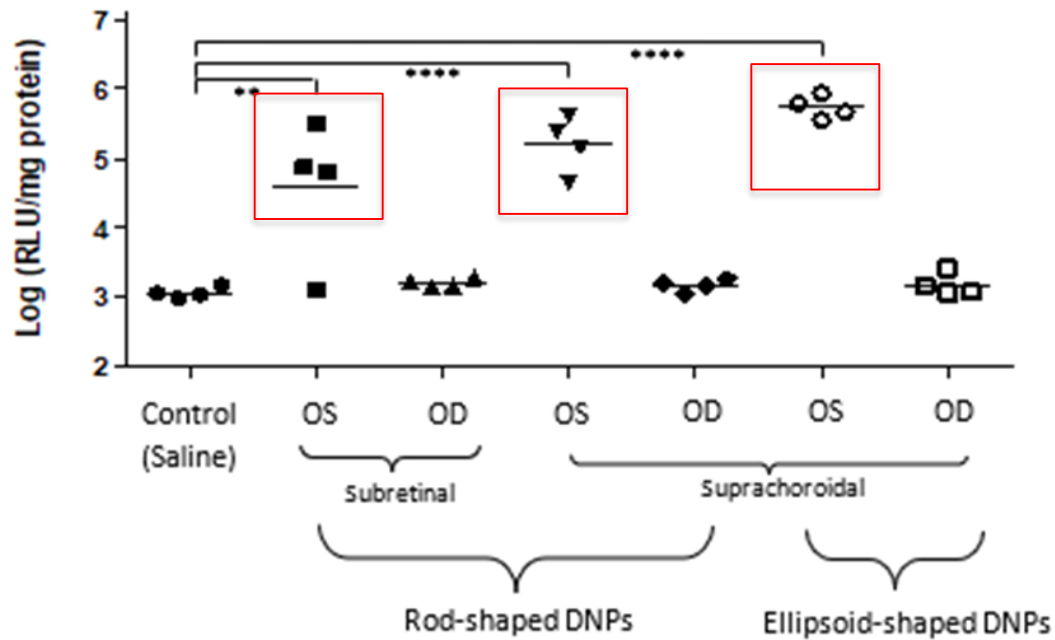


1-way ANOVA, $p = 0.0088$.
Bonferroni's multiple comparison test: * $p < 0.05$, ** $p < 0.01$

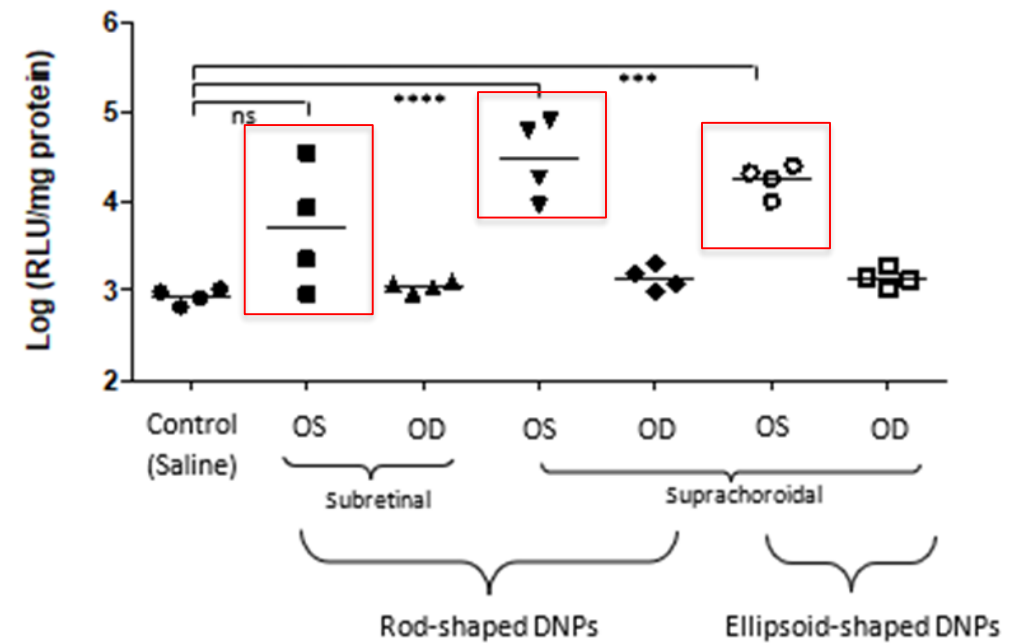
Rabbit: DNA Nanoparticles Transfect the RPE + Choroid and Retina



Non Viral-Luciferase, Rabbit
CHOROID



Non Viral-Luciferase, Rabbit
RETINA



OS: Dosed OD: Undosed	Bonferroni's multiple comparison test: ** p<0.01, *** p<0.001, **** p<0.0001 ns, non-significant
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Study Summary

- Luciferase activity observed in the **retina and RPE+choroid**
- In rabbits, SC injection **comparable to subretinal injections** of luciferase DNPs produced activity
- SC injections of DNPs were **generally well-tolerated** across groups in both species

- Safety
 - SC injection of DNPs may address an unmet need in ocular gene delivery
 - Non-immunogenic, **potential for repeat dosing**
- Efficacy
 - Higher doses may be used to enhance transfection
 - DNPs can transfer **large genes** which may allow for gene therapy in the most common inherited retinal diseases (IRDs) such as **Stargardt** disease and **Usher syndrome**

- **SC injections of DNPs offer the potential for a safer and efficient delivery method**