Nanoscale activated carbons for intrastromal controlled drug release

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CRS 2025 ANNUAL MEETING & EXPOSITION
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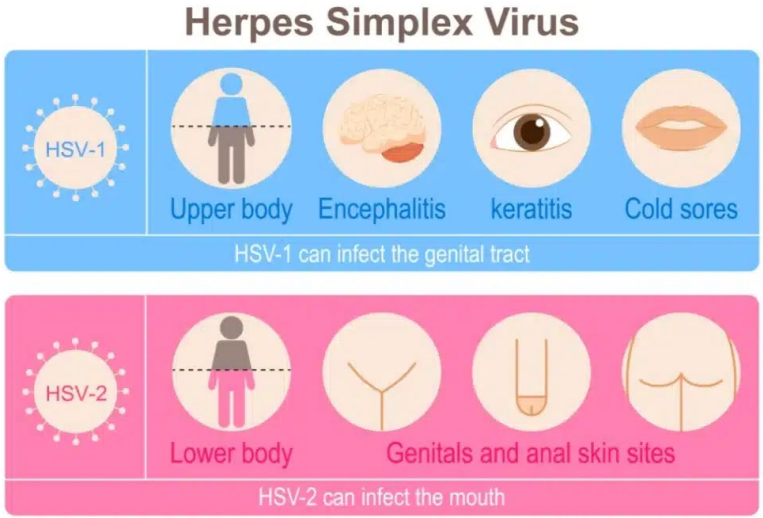
NEXT-GENERATION DELIVERY INNOVATIONS

NO CONFLICTS OF INTEREST TO DECLARE

HSV- Herpes Simplex Virus

- Two main types: HSV-1 and HSV-2
- Highly contagious → direct contact
- Common virus → 80% of people are carriers without knowledge
- Neurotropic virus = having an affinity to nerve cells
- Latency and reactivation
  - due to stress, illness, immune suppression
  - ↑ risk of repeated infections + serious complications

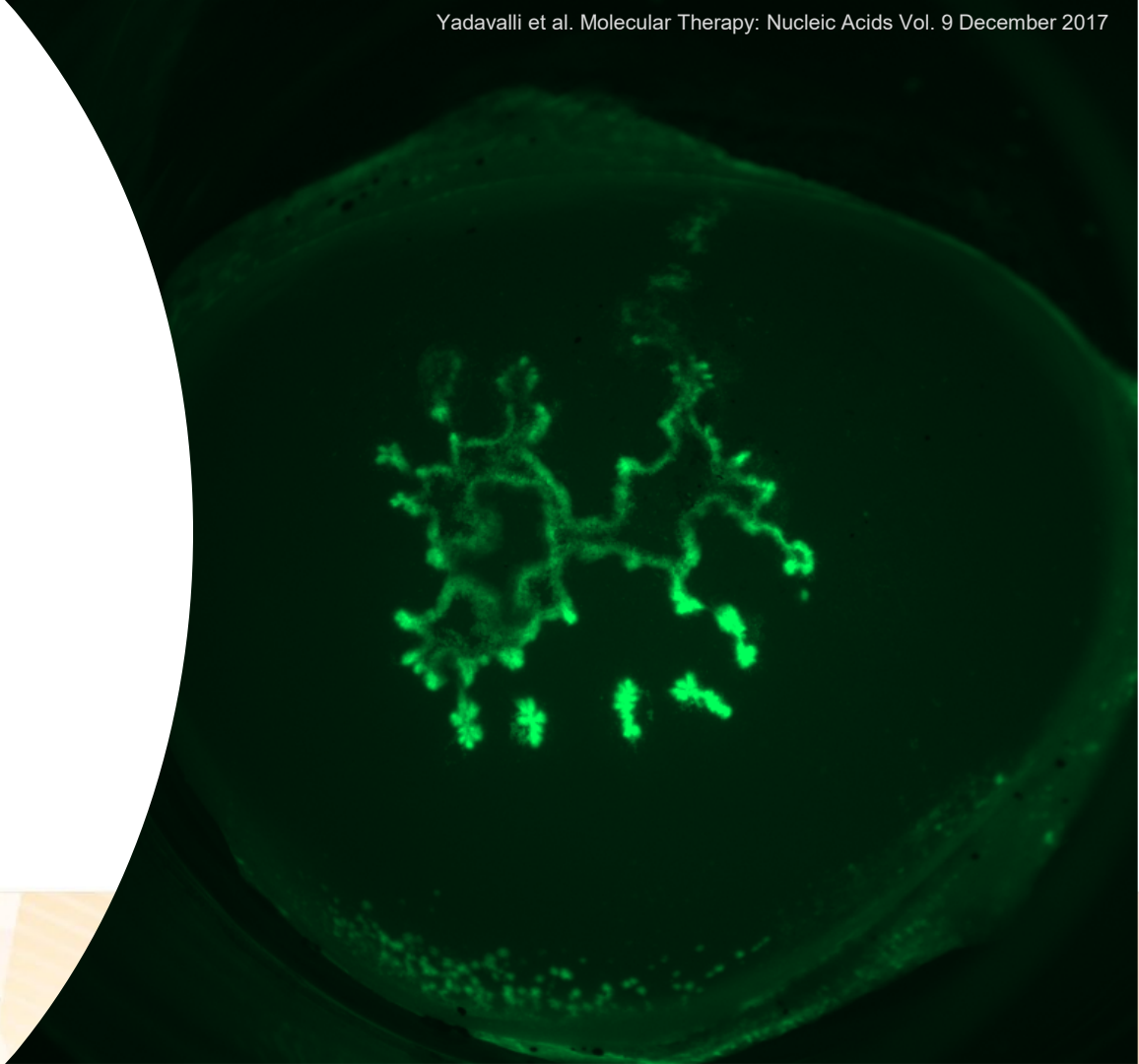


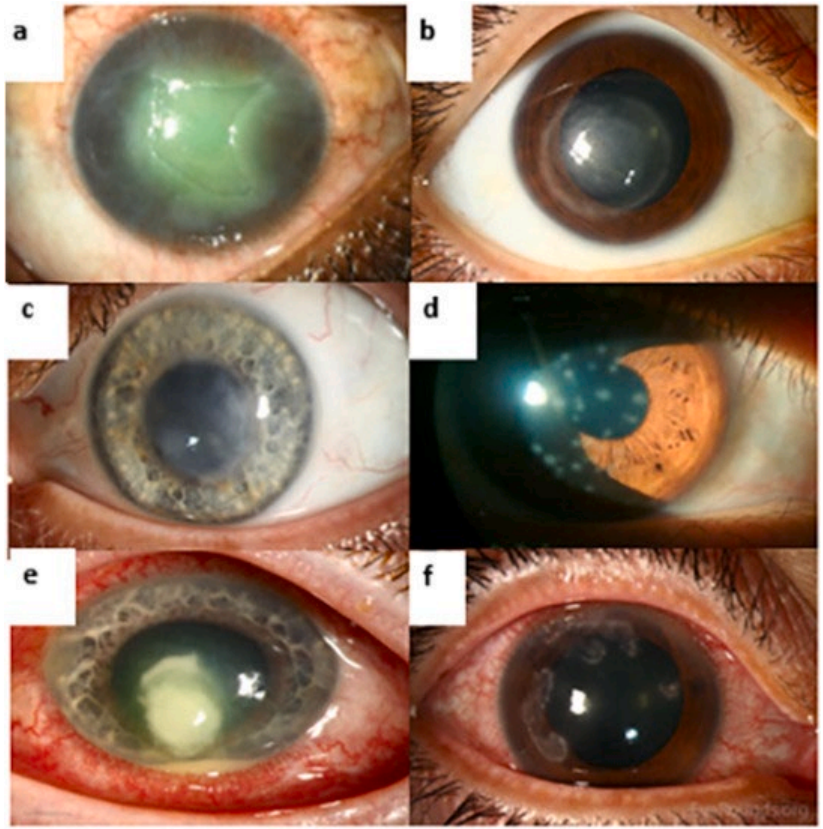
Yadavalli et al. Molecular Therapy: Nucleic Acids Vol. 9 December 2017

Herpes Simplex Virus

Clinical manifestations:

- 1. Herpes Labialis (eg, cold sores, fever blisters)
- 2. Ocular Herpes
- 3. Herpes Genitalis
- 4. Herpes whitlow
- 5. Herpes gladiatorum
- 6. Meningitis
- 7. Encephalitis
- 8. Neonatal herpes





- Viral Keratitis (VK) is the most prevalent form of infectious keratitis with over 1 million annual cases of herpetic keratitis alone.
- VK can cause four different types of keratitis: epithelial, stromal, endothelial, and neurotrophic keratopathy.
- Necroptosis of the corneal tissue and immune cell infiltration contribute to the viral keratitis.
- Nucleoside analogs and glucocorticoids are primary treatment options for patients with VK

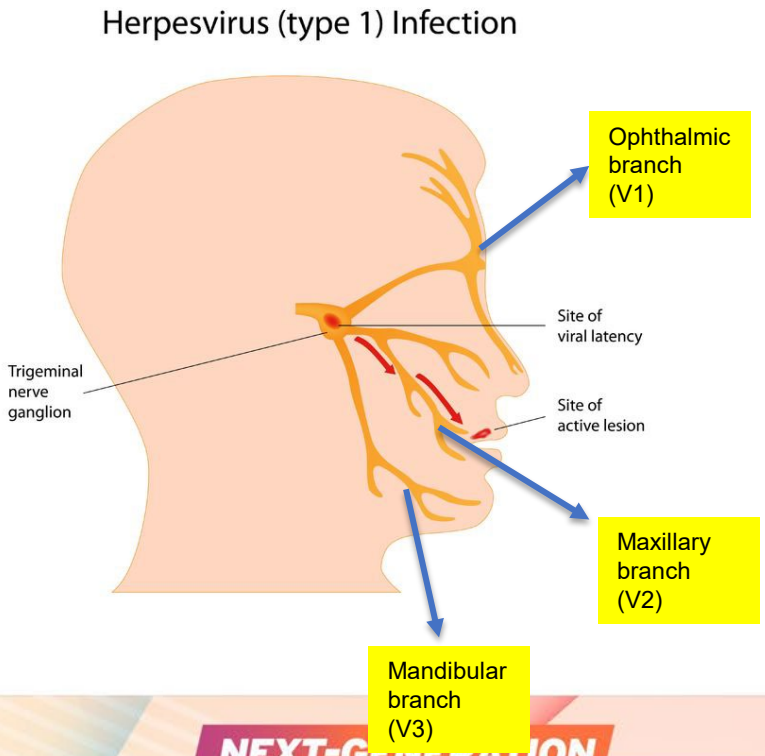
Representative keratitis pictures of human eyes. (a) Fluorescein stained images of herpes simplex corneal keratitis (Azher et al., 2017). (b) A close-up whole eye image of human eye showing herpetic disciform keratitis (Vislisel, 2015). (c) Varicella zoster virus disciform keratitis (Vislisel, 2014). (d) Slit-lamp imaging of adenoviral keratitis (Wikipedia, 2020). (e) Image of a human eye with fungal keratitis caused due to Aspergillus (Vislisel, 2016). (f) Slit-lamp photography of Nocardia keratitis caused by Nocardia farcinia (Scruggs, 2017).

Site of Latency: Trigeminal Ganglion (TG)

- neural clusters found behind our cheekbones
- 3 main routes
- carry sensory information from face to brain
- HSV site of entry: mouth, nose, eyes.

Immune Evasion

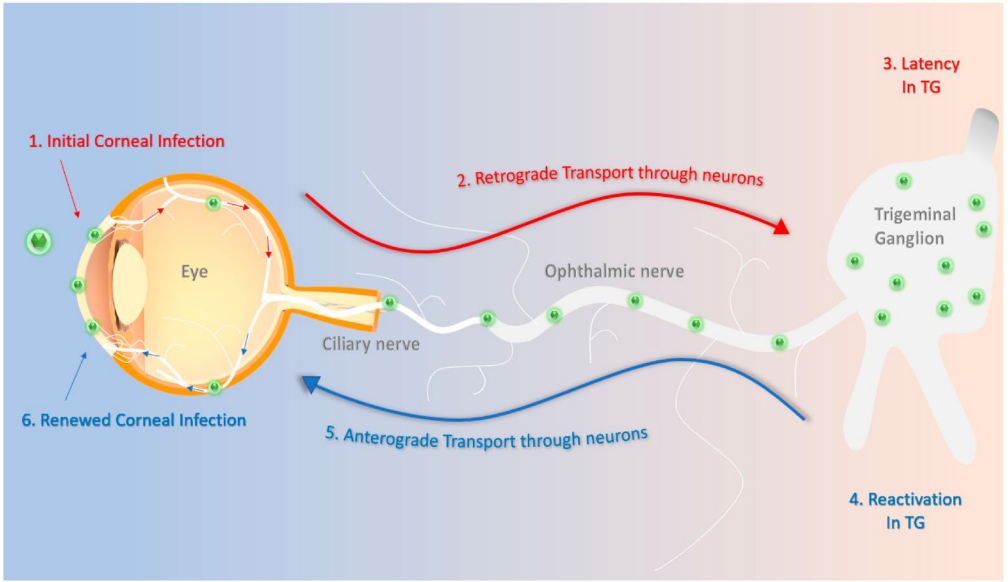
1. TG= immune-privileged site
   - Fewer immune cells present → control inflammation & protect sensitive neural tissue
2. Latency-Associated Transcript (LAT) = non-coding RNA
   - Downregulates pro-apoptotic factors = blocks apoptosis of infected neurons
   - Infected neurons are long-lived + less exposed to the immune system



HSV- Anterograde Transport

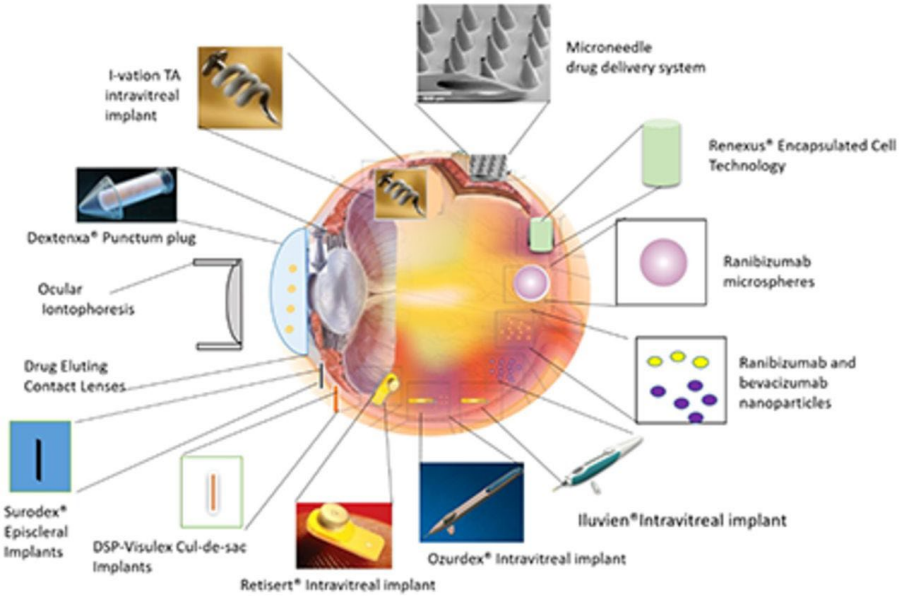
Herpes Simplex Keratitis (HSK)
HSV reactivation from ophthalmic branch of TG

- Repeated episodes – corneal scarring and vision loss
- Most common cause of infectious blindness in developed countries (CITE)

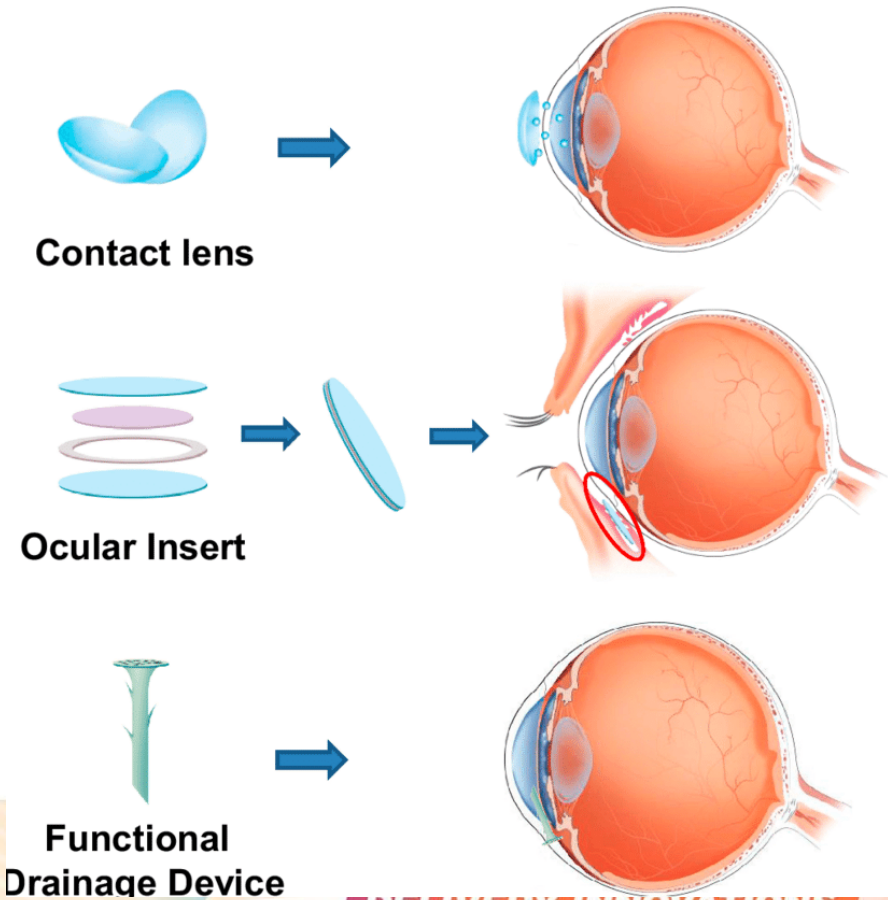


- **Current Alternatives**
  - **Oral Dosage**
    - Reduced frequency than topical
    - Systemic toxicity over time
    - Higher antiviral resistance
  - **Topical Dosage**
    - Not prescribed often
    - Requires 4-9 drops every day
    - Gels can only be applied in the night

Ocular Drug Delivery Systems

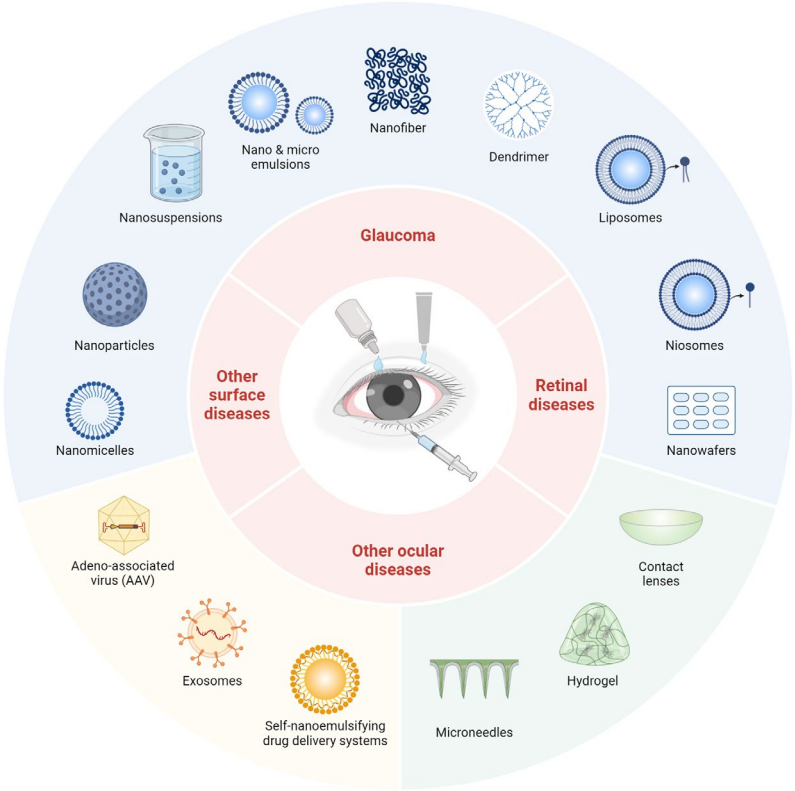


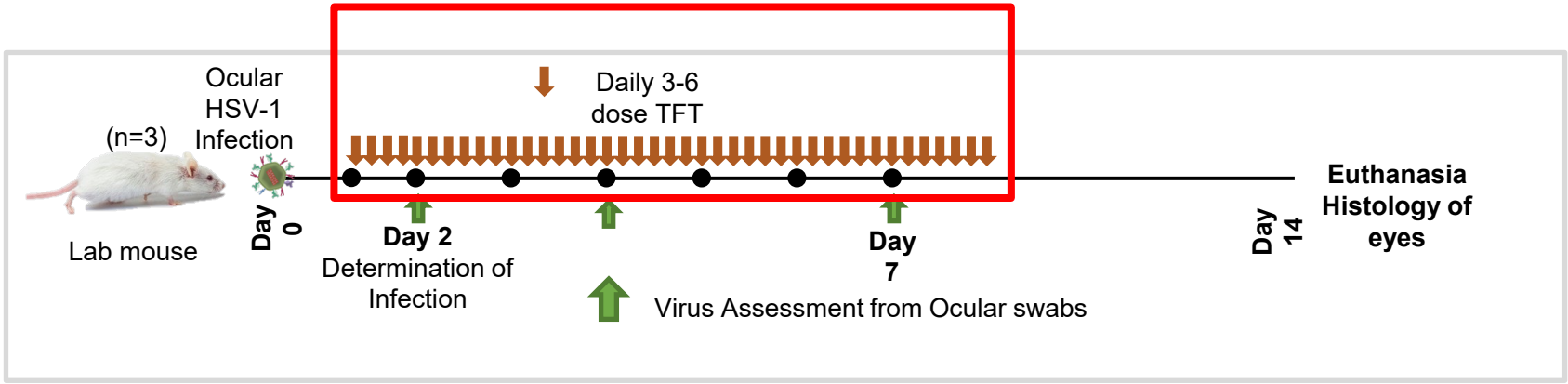
Ocular Drug Delivery: Present Innovations and Future Challenges
Journal of Pharmacology and Experimental Therapeutics September 2019, 370 (3) 602-624

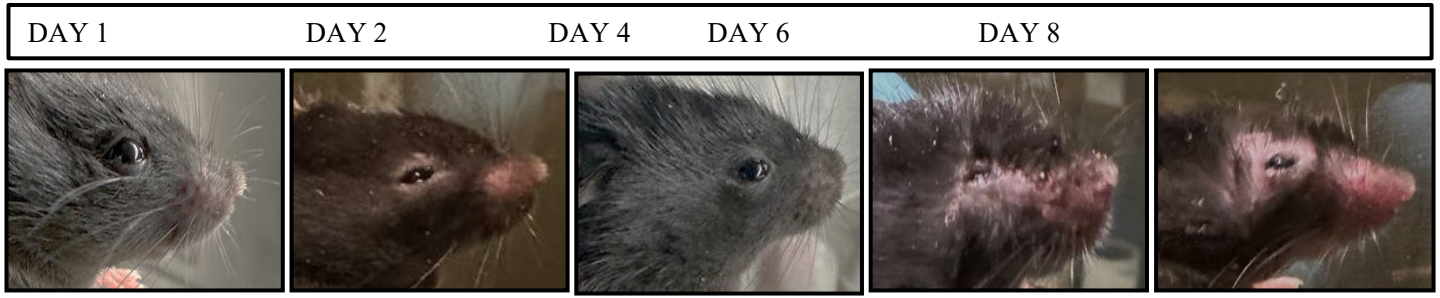


https://doi.org/10.2147/IJN.S254792

Topical Sustained Release Systems







Invest. Ophthalmol. Vis. Sci. 2024;65(3):7. https://doi.org/10.1167/iovs.65.3.7.

Dendrimer

Dendrimer Type	Drug Type	Typical DLE Range (%)
Polyamidoamine (PAMAM) dendrimers	Hydrophobic and hydrophilic drugs	10-40
Polyglycerol dendrimers	Hydrophilic drugs	5-20
Hyperbranched polymers	Hydrophobic and hydrophilic drugs	10-30

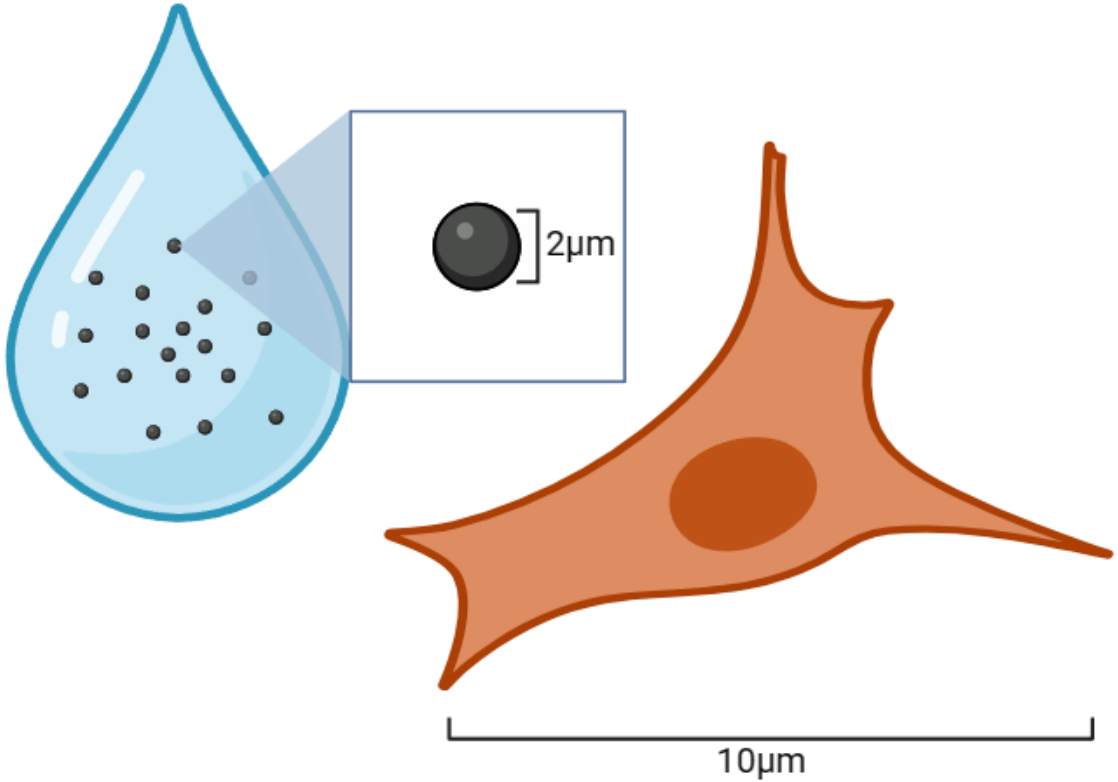
Liposome

Liposome Type	Drug Type	Typical DLE Range (%)
Conventional liposomes	Hydrophobic drugs	10-30
Stealth liposomes (PEGylated)	Hydrophobic drugs	15-40
Cationic liposomes	Hydrophilic and hydrophobic drugs	5-30

Polymer

Polymer	Drug Type	Typical DLE Range (%)
Poly(lactic-co-glycolic acid) (PLGA)	Hydrophobic drugs (e.g., paclitaxel, docetaxel)	10-30
Poly(ε-caprolactone) (PCL)	Hydrophobic drugs	15-40
Poly(vinylpyrrolidone) (PVP)	Hydrophilic and hydrophobic drugs	10-50

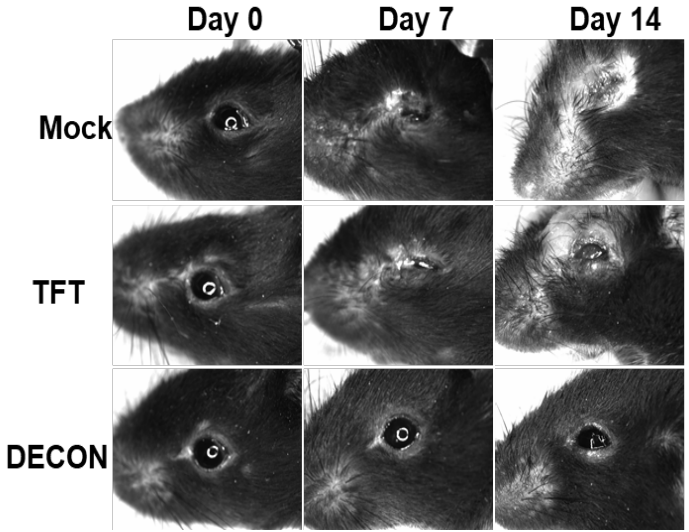
*Values are an approximation based on literature search



Known for its trapping ab
Highest known adsorptic
Highest known surface a
Non-toxic. Applied as ey

Science Advances

Science Advances 14 Aug 2019:
Vol. 5, no. 8, eaax0780
DOI: 10.1126/sciadv.aax0780



Trifluridine (TFT), FDA approved topical treatment requires **6-9 doses/day**. When dosed alternate day

DECON was dosed **once every 2 days**

Treatment regimens for anti-inflammatories are daunting

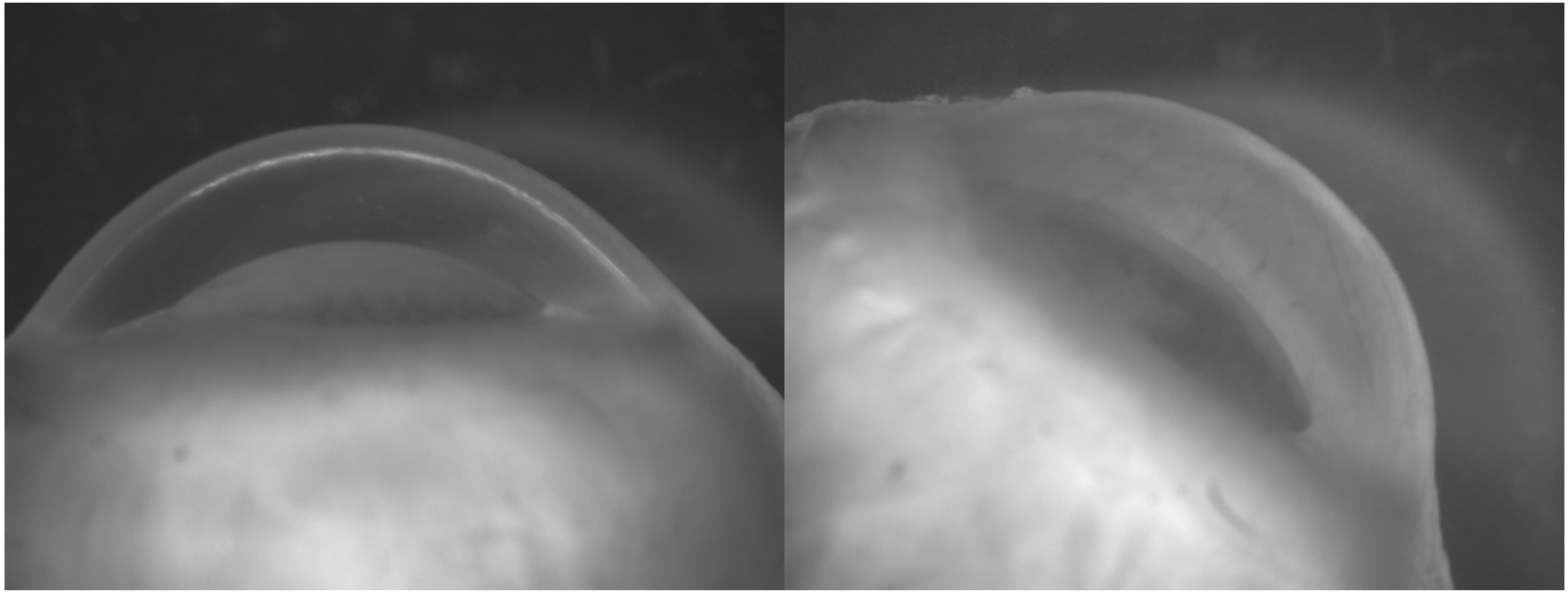
Example corticosteroid Eye Drops Regimen:
1.Week 1 (Acute Phase):
Apply 1 drop every 1-2 hours during waking hours.

2.Week 2 (Moderation Phase):
Apply 1 drop every 4-6 hours.

3.Week 3 (Tapering Phase):
Apply 1 drop every 8-12 hours.

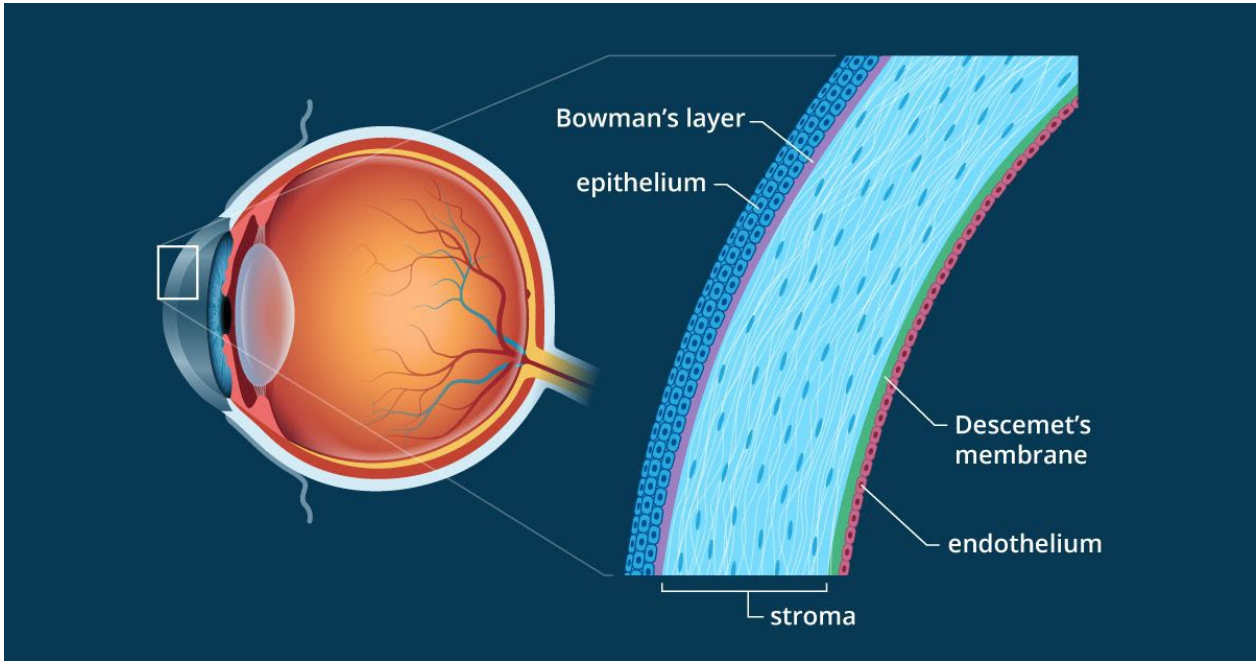
4.Week 4 (Maintenance Phase):
Apply 1 drop once daily or every other day until completely stopped.

Corneal Stroma is the site of most corneal inflammation due to HSV-1

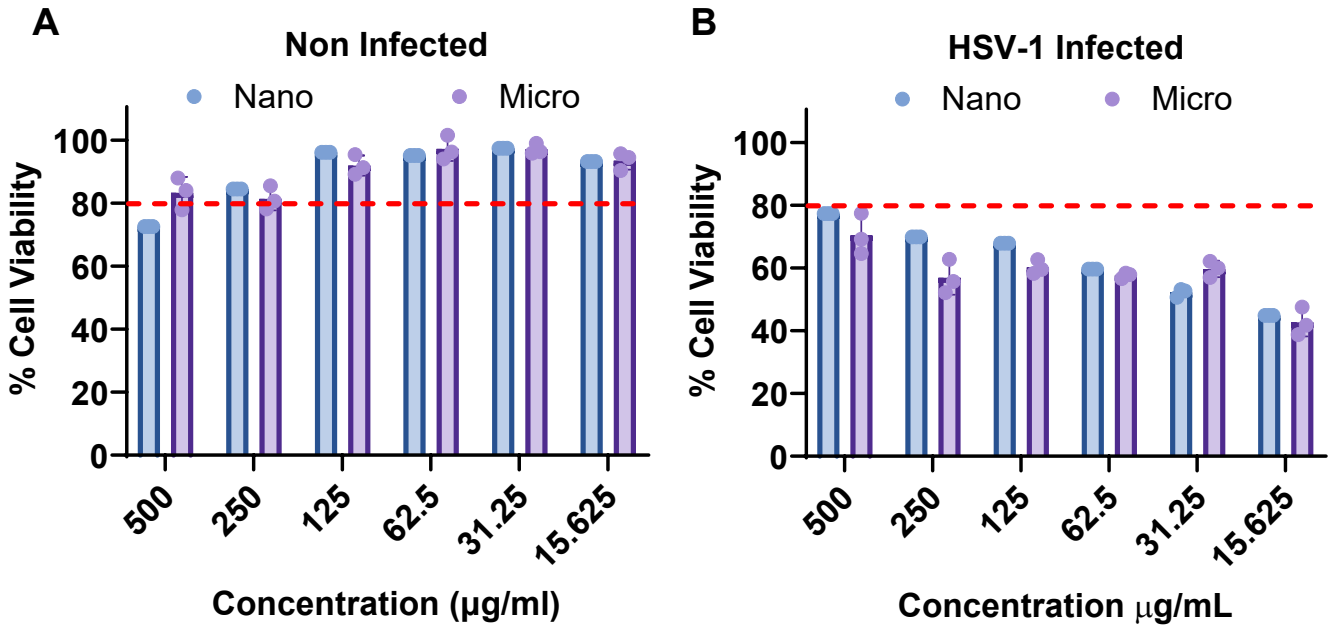


https://www.allaboutvision.com/eye-care/eye-anatomy/eye-structure/cornea/

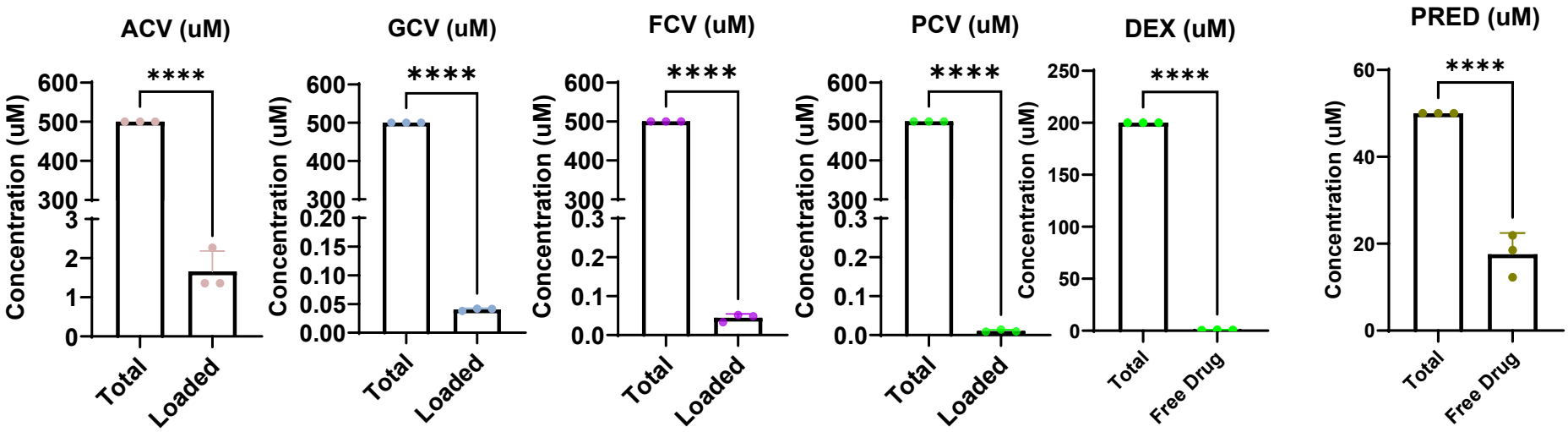
2 micron particles will not be able to cross over into the stroma



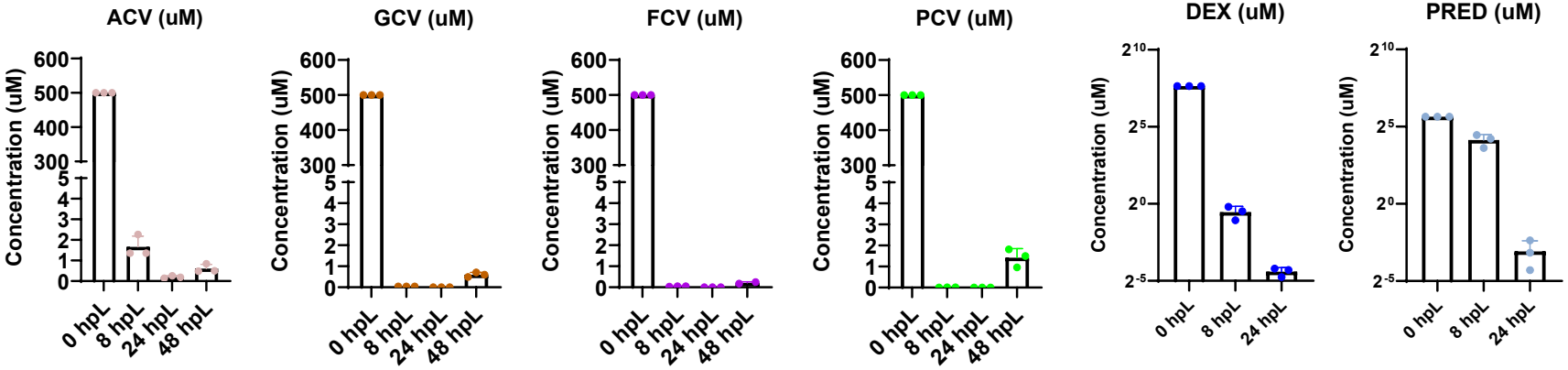
https://www.allaboutvision.com/eye-care/eye-anatomy/eye-structure/cornea/

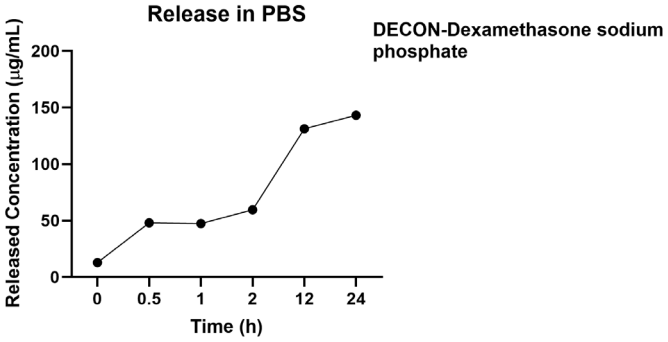

A
Non Infected
Nano
Micro
% Cell Viability
100
80
60
40
20
0
500
250
125
62.5
31.25
15.625
Concentration (µg/ml)
B
HSV-1 Infected
Nano
Micro
% Cell Viability
100
80
60
40
20
0
500
250
125
62.5
31.25
15.625
Concentration µg/mL

DRUG LOADING

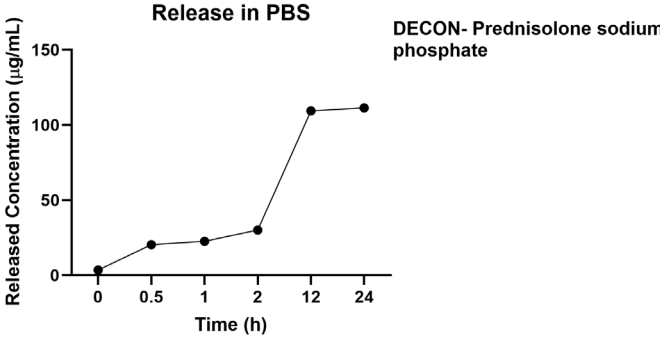


PASSIVE DRUG RELEASE

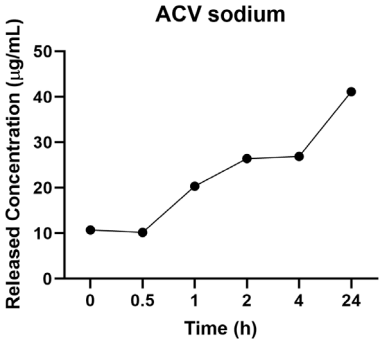


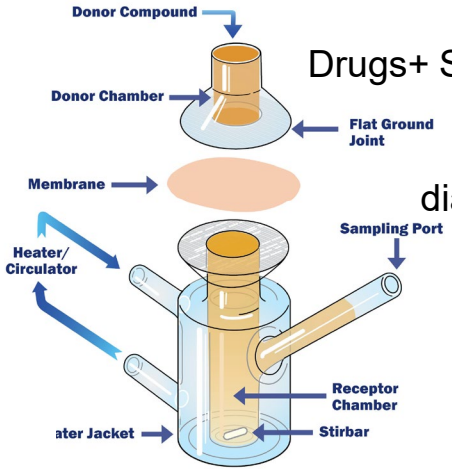


DECON-Dexamethasone sodium phosphate



DECON- Prednisolone sodium phosphate

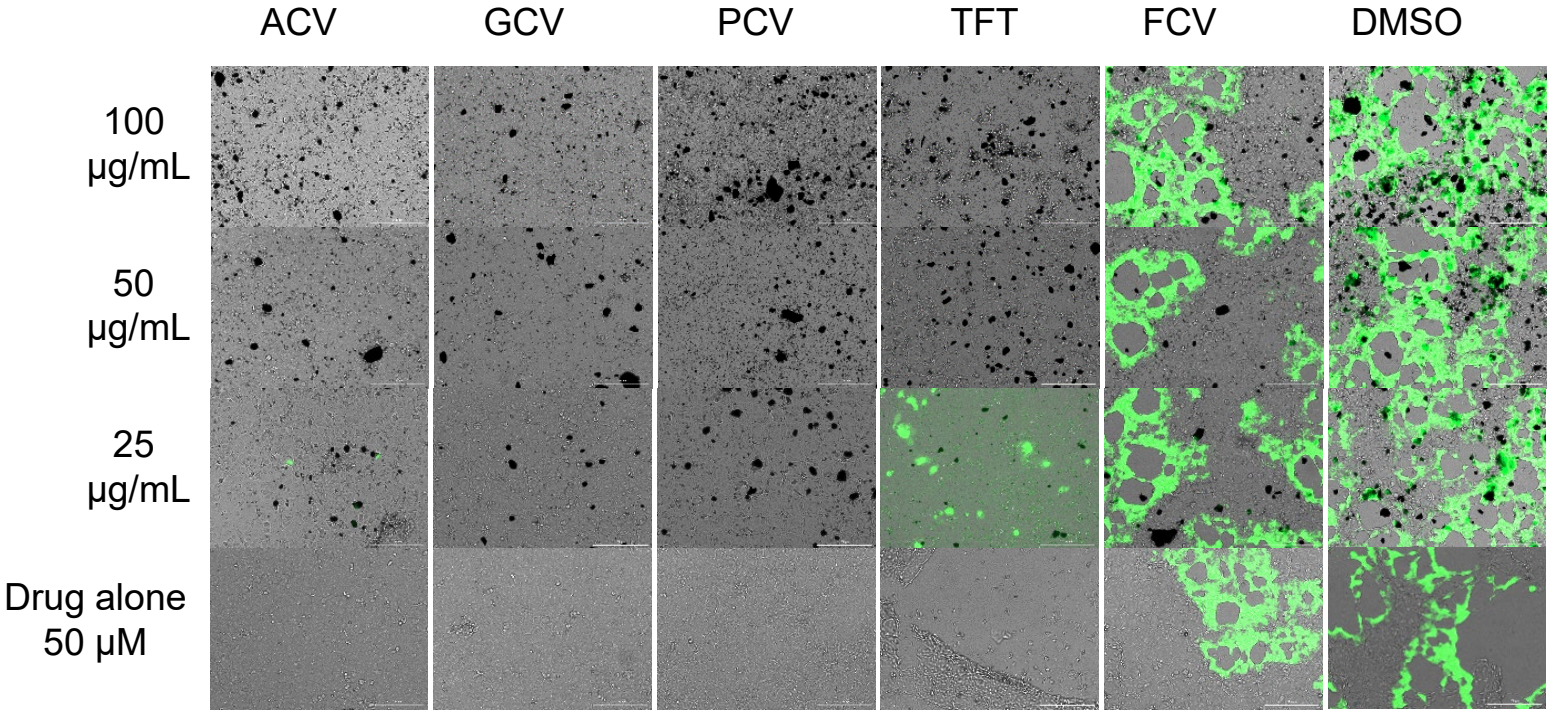


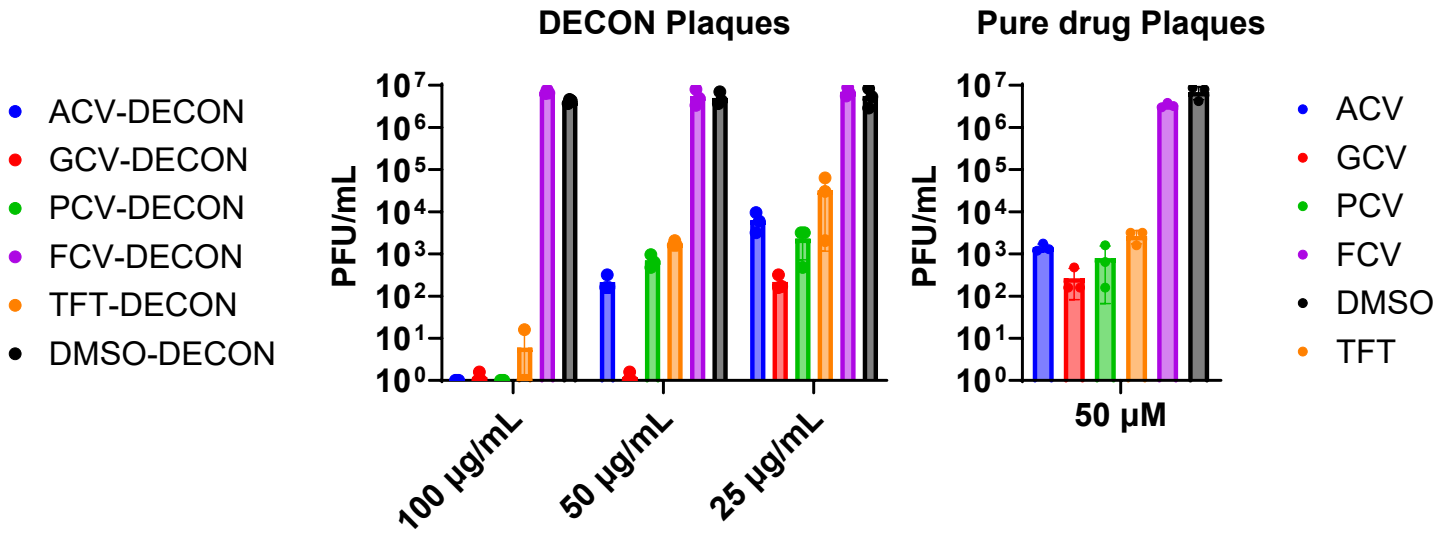


Drugs+ Simulated tear fluid

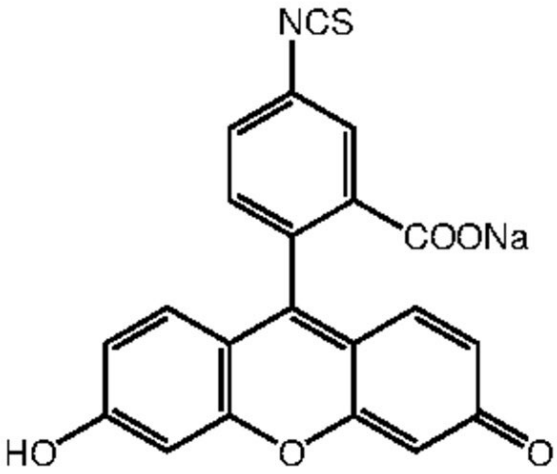
Human eye or dialysis membrane

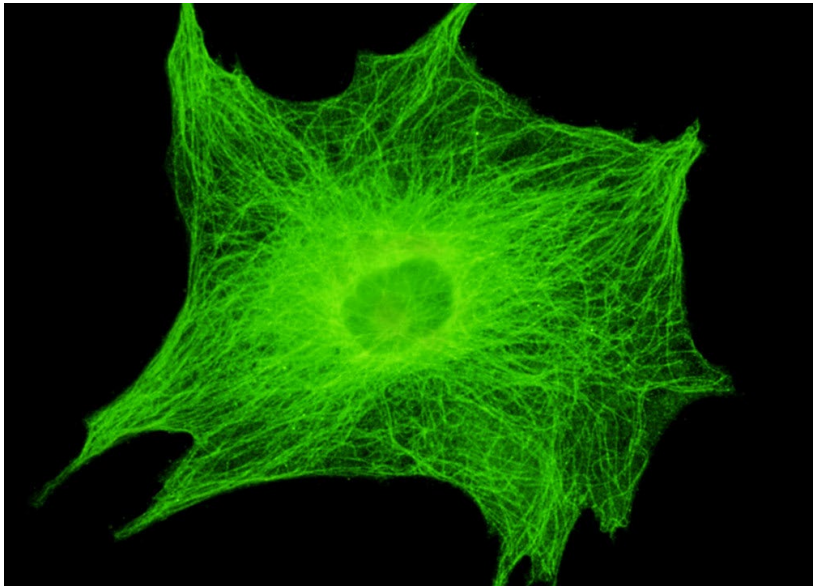
PBS


ACV
GCV
PCV
TFT
FCV
DMSO
100 µg/mL
50 µg/mL
25 µg/mL
Drug alone 50 µM


ACV-DECON
GCV-DECON
PCV-DECON
FCV-DECON
TFT-DECON
DMSO-DECON
DECON Plaques
PFU/mL
10^7
10^6
10^5
10^4
10^3
10^2
10^1
10^0
100 µg/mL
50 µg/mL
25 µg/mL
Pure drug Plaques
PFU/mL
50 µM
ACV
GCV
PCV
FCV
DMSO
TFT

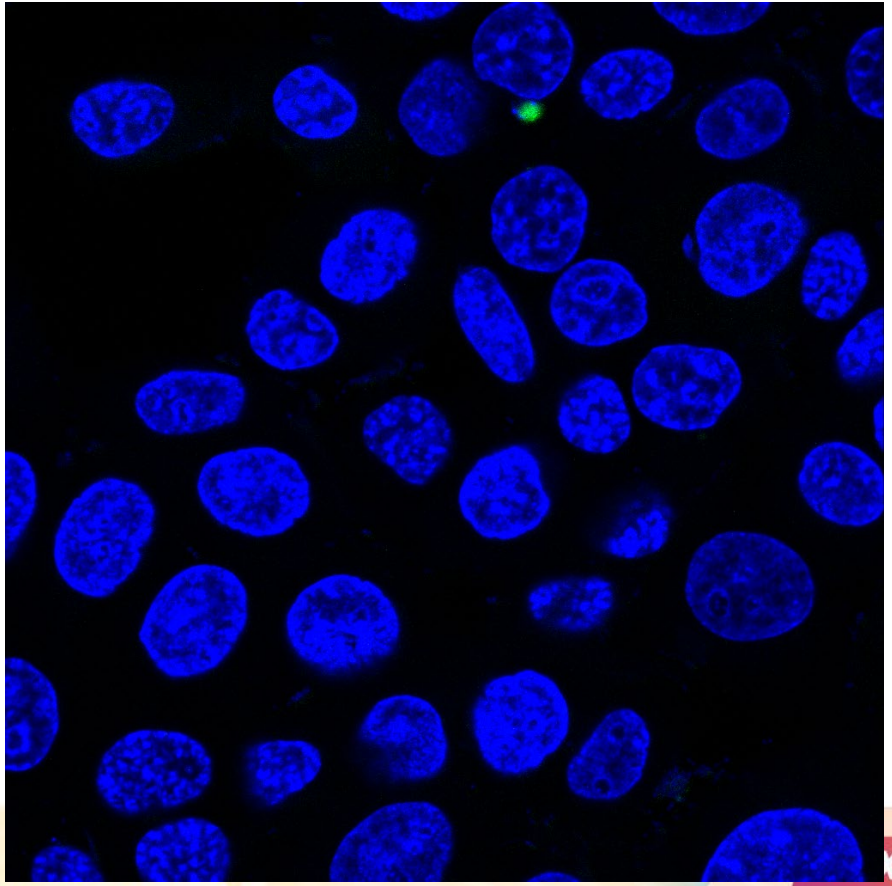
Fluorescein





http://www.microscopyu.com/gallery-images/indian-muntjac-skin-cell-tubulin-with-fluorescein

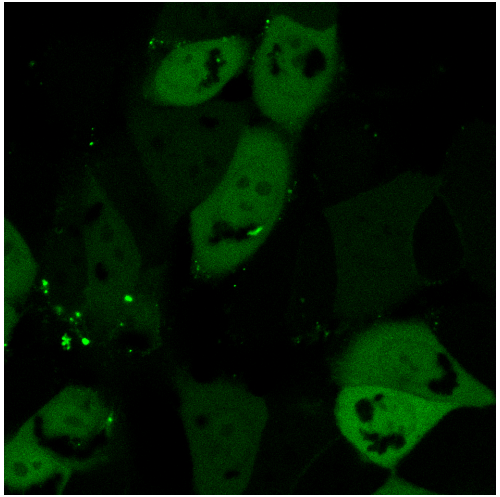
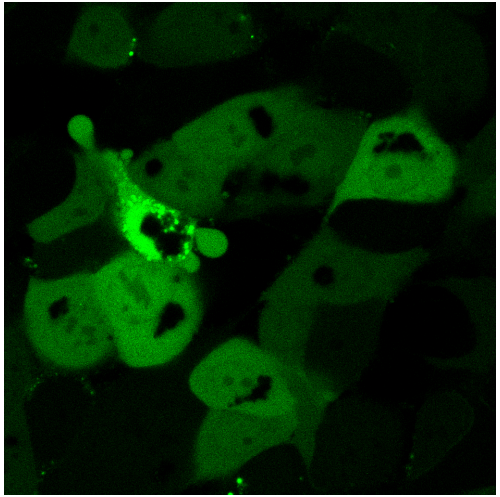
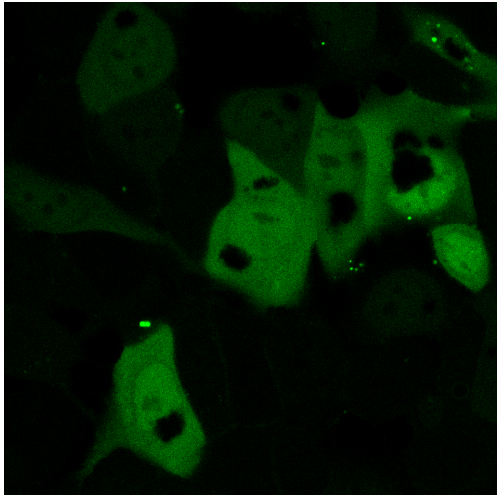
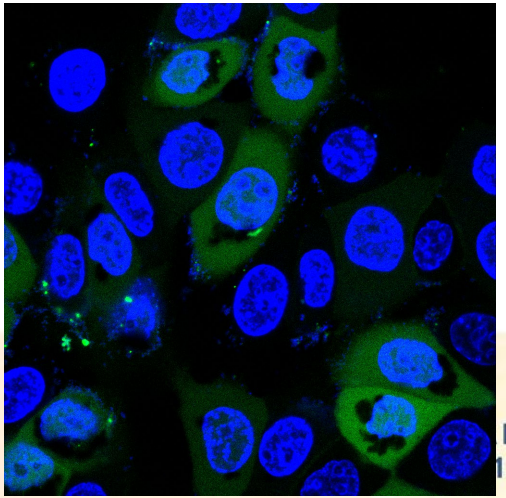
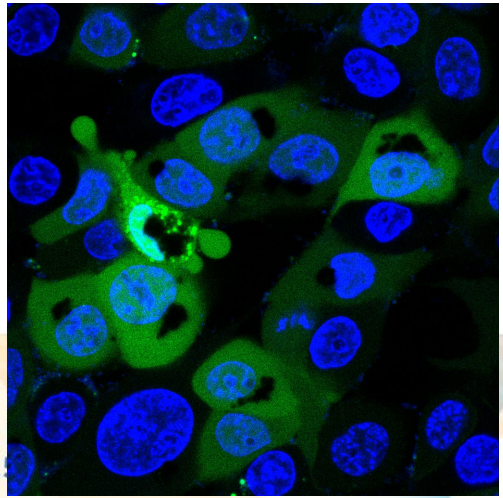
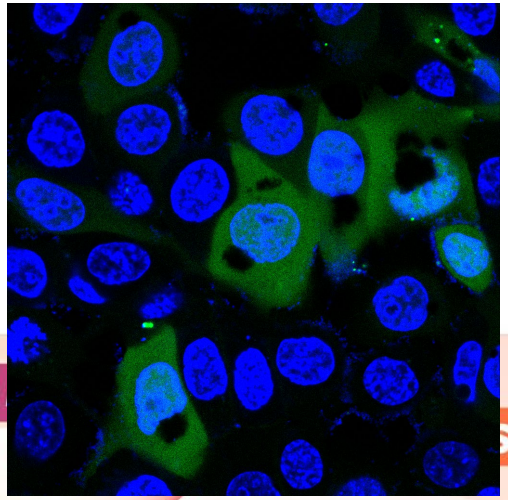
FITC only



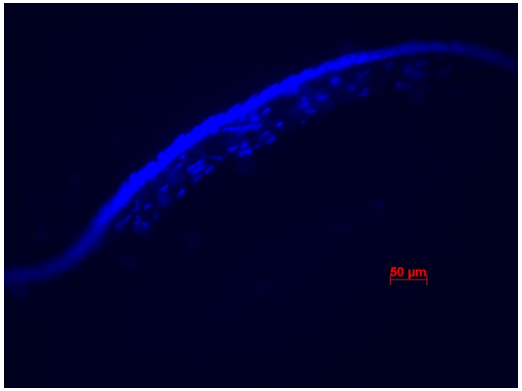
Under Review

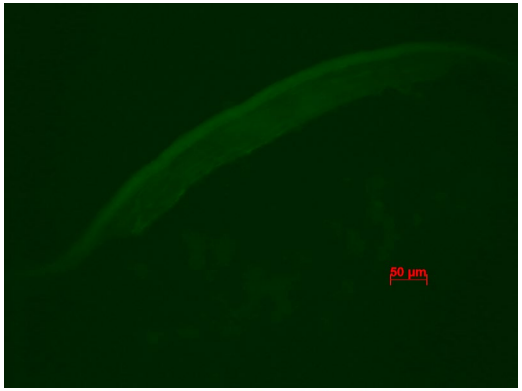
Under Review

FITC Loaded Nano Carbon

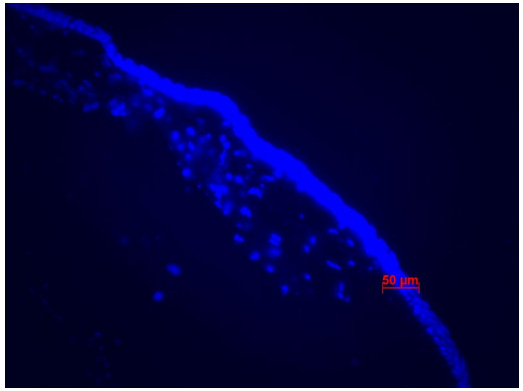







FITC Loaded nDECON





Non Treated



n=3 mice per group

Pharmacokinetics in Murine Models

Dexamethasone (5 µg Dose):

Retention in murine eyes was observed over 24 hours, with peak concentrations (~277 ng/g) at 0.5 hours and diminishing levels over time.

Prednisolone (50 µg Dose):

Higher ocular retention (1105 ng/g) was observed compared to dexamethasone, with significant decline over time but better persistence at 24 hours.

Higher ocular retention in murine models

5 µL of Dexamethasone SP alone added at 0.1% (5 µg)

Time (h)	Concentration (ng/g)														Mean (ng/g)
	Mouse 1	Mouse 2	Mouse 3	Mouse 4	Mouse 5	Mouse 6	Mouse 7	Mouse 8	Mouse 9	Mouse 10	Mouse 11	Mouse 12	Mouse 13	Mouse 14	Mouse 15	
0.5	BLOQ	18.1	20.1													19.1
2				BLOQ	BLOQ	6.32										NA
4							BLOQ	BLOQ	BLOQ							NA
8										BLOQ	BLOQ	BLOQ				NA
24													BLOQ	BLOQ	BLOQ	NA

5 µL of Dexa-DECON at 0.1mg/mL (~1 µg of API)

Time (h)	Concentration (ng/g)														Mean (ng/g)
	Mouse 16	Mouse 17	Mouse 18	Mouse 19	Mouse 20	Mouse 21	Mouse 22	Mouse 23	Mouse 24	Mouse 25	Mouse 26	Mouse 27	Mouse 28	Mouse 29	Mouse 30	
0.5	338	308	184													277
2				27.8	51.6	45.6										**41.7**
4							21.8	19.5	25.5							**22.3**
8										19.20	14.1	53.6				**25.6**
24													5.3	4.7	21.2	**10.3**

Higher ocular retention in murine models

5 µL of Prednisolone SP alone added at 1% (50 µg)

Time (h)	Concentration (ng/g)														Mean (ng/g)
	Mouse 1	Mouse 2	Mouse 3	Mouse 4	Mouse 5	Mouse 6	Mouse 7	Mouse 8	Mouse 9	Mouse 10	Mouse 11	Mouse 12	Mouse 13	Mouse 14	Mouse 15	
0.5	7.36	26.1	39.1													24.2
2				BLOQ	BLOQ	BLOQ										NA
4							BLOQ	BLOQ	BLOQ							NA
8										BLOQ	BLOQ	BLOQ				NA
24													BLOQ	BLOQ	BLOQ	NA

5 µL of Pred-DECON at 0.1mg/mL (~10 µg of API)

Time (h)	Concentration (ng/g)														Mean (ng/g)
	Mouse 16	Mouse 17	Mouse 18	Mouse 19	Mouse 20	Mouse 21	Mouse 22	Mouse 23	Mouse 24	Mouse 25	Mouse 26	Mouse 27	Mouse 28	Mouse 29	Mouse 30	
0.5	1436	740	1140													1105
2				64.4	26.9	36.4										**42.6**
4							9.00	12.2	9.00							**10.1**
8										4.76	12.5	28.5				**15.2**
24													BLOQ	BLOQ	BLOQ	NA

Conclusions and Future Work

- Nanosized carbons are able to penetrate to the corneal stroma
- nDECONs are able to deliver the payload to murine stroma
- Future work will have to see if this level of increased penetration causes any toxicity or fibrosis
- Larger animal modes (rabbits) to test if the penetration is deep enough to reach the stroma.

Acknowledgements

OD3 Lab Members
Dr. Ankita Sarkar
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Maherah Shaik
Mannat Singh
Mansi Bagri

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Dr. Abhijit Date
Dr. Alexander Yarin
Dr. Elmira Jalilian
Dr. Pooja Bhat

OVCR
CCTS

Research to Prevent Blindness

NIH

R01EY034508
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QUESTIONS

Open to collaborations

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