Novel treatments for retinal degeneration: Ocular bio-distribution and treatment efficacy of lipid nanocapsules and liposomes

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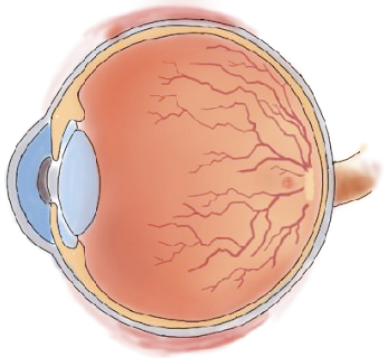
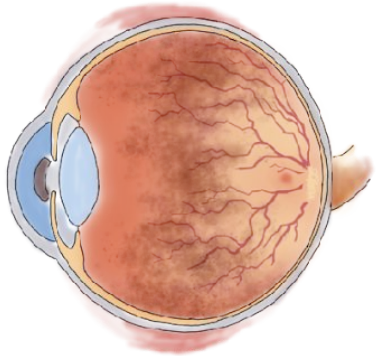
Advanced Delivery Science

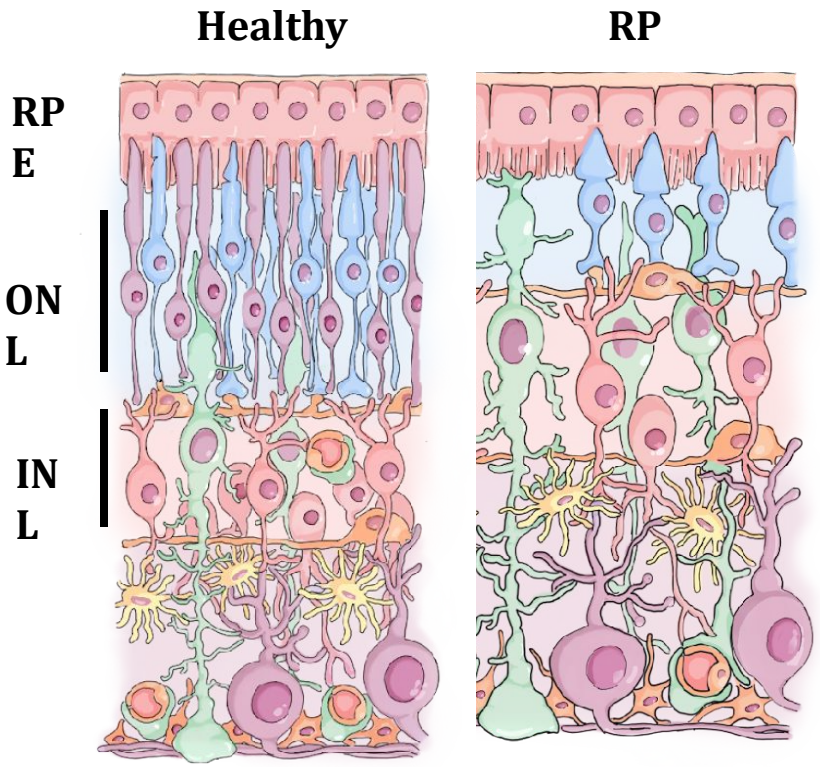
Retinitis Pigmentosa (RP)

Healthy eye



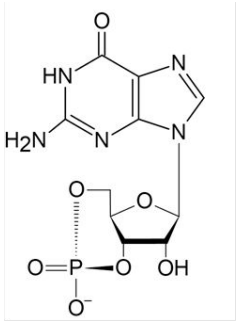
RP eye



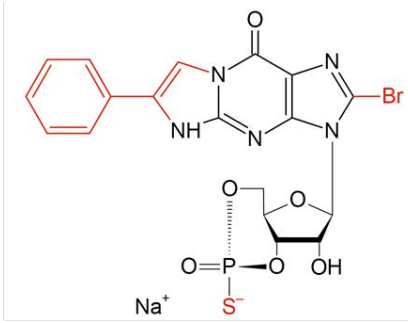


Drawings by Yu Zhu

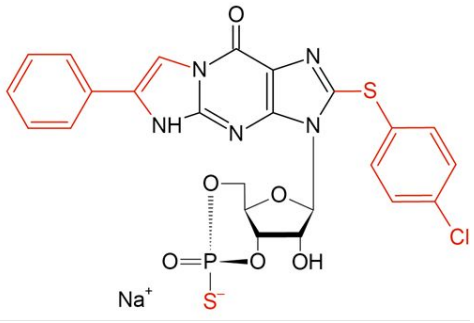
Novel treatment for RP: therapeutic cGMP analogues



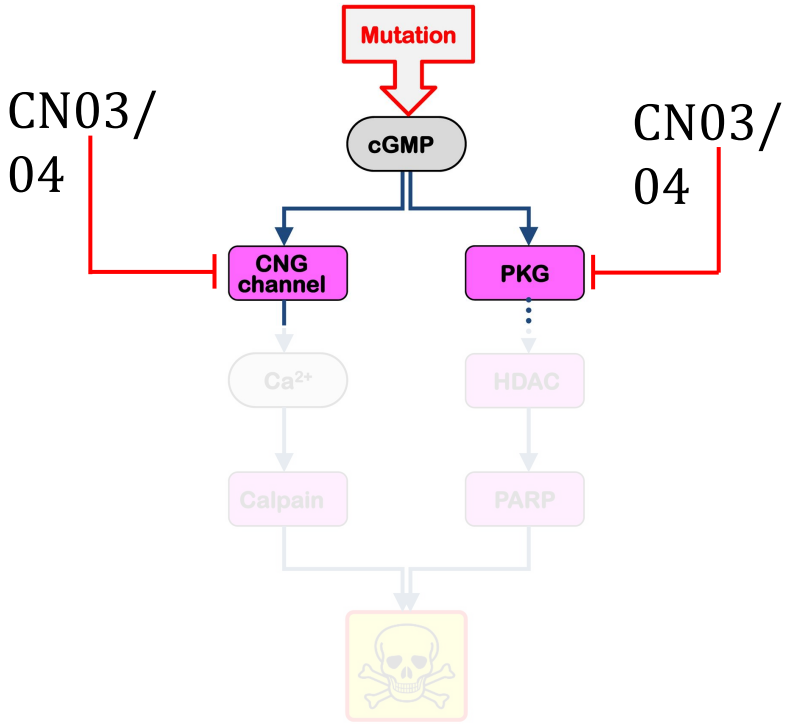
Cyclic guanosine monophosphate
(cGMP)



Rp-8-Br-PET-cGMPS
(CN03)



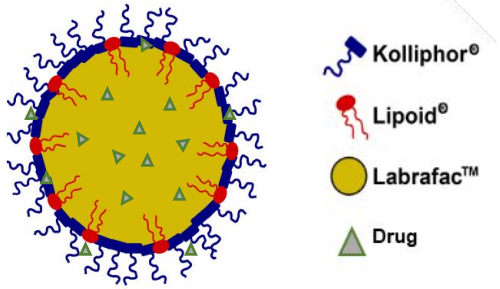
Rp-8-pCPT-PET-cGMPS
(CN04)



Arango-Gonzalez, PLoS ONE, 2014.

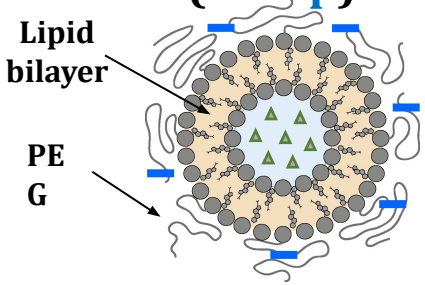
Testing three different ocular drug delivery systems

Lipid nanocapsule (LNC)



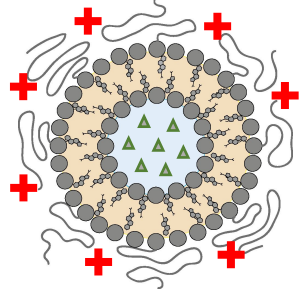
LNC	
Hydrodynamic diameter (nm)	61 ± 1
ζ-potential (mV)	– 2.5 ± 1.1
EE of CN03 (%)	69 ± 0.5

Anionic PEGylated liposomes (An-Lp)



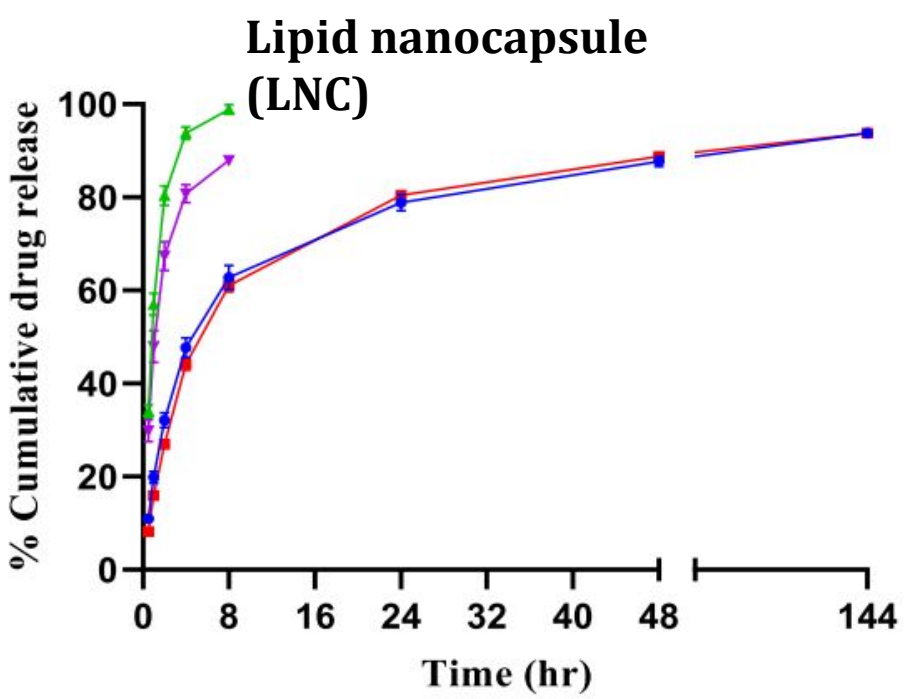
An-Lp	
Hydrodynamic diameter (nm)	124 ± 5
ζ-potential (mV)	– 34 ± 3
EE of CN04 (%)	74 ± 11
EE of CN03 (%)	27 ± 7

Cationic PEGylated liposomes (Cat-Lp)



Cat-Lp	
Hydrodynamic diameter (nm)	133 ± 2
ζ-potential (mV)	41 ± 1
EE of CN04 (%)	73 ± 4

In vitro release profiles



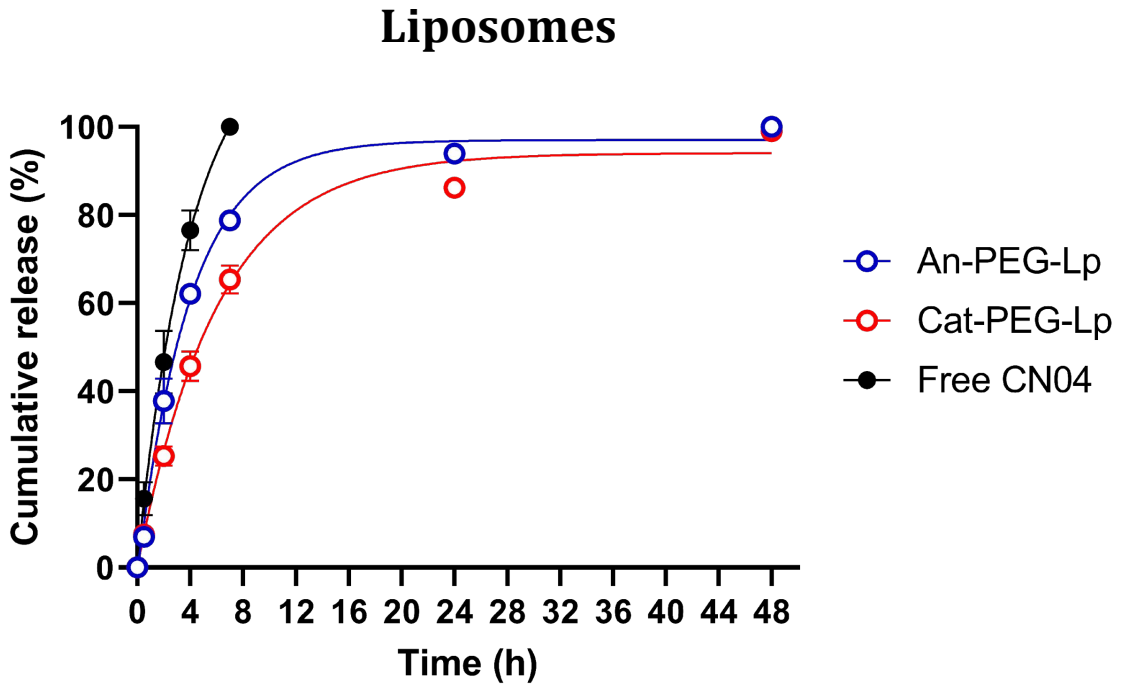


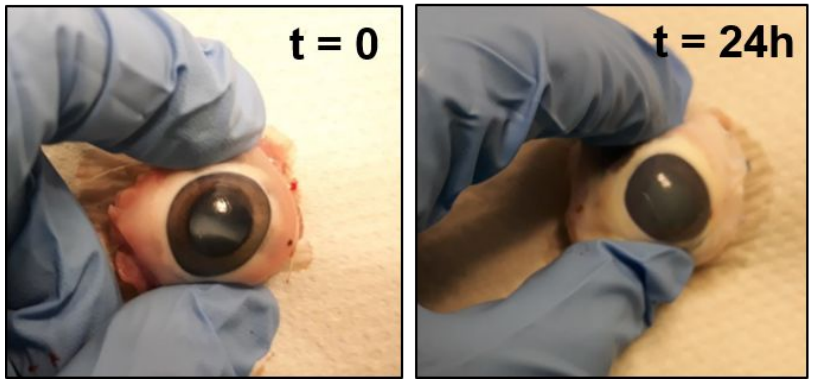
Fig. 5. *In vitro* release testing of free drug in phosphate buffer (–•–), free drug in hyaluronic acid (–•–), drug loaded LNCs (F6) in phosphate buffer (–•–) and drug loaded LNCs (F6) in hyaluronic acid (–•–). (Mean ± SD, n = 3).

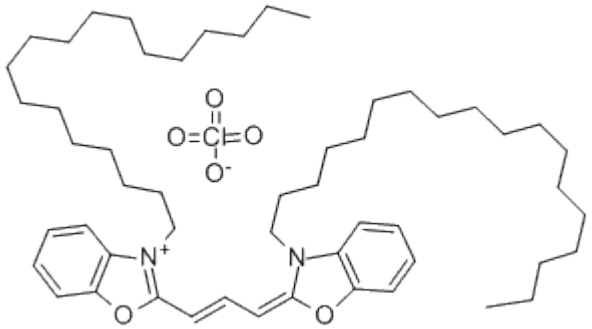
Urimi et al., International journal of pharmaceutics, 2021

Intra-ocular bio-distribution in ex vivo porcine eyes

- Porcine eyes obtained from slaughterhouse
- Intravitreal injection of DiO-loaded particles (50 µL)
- 24 h incubation (RT)

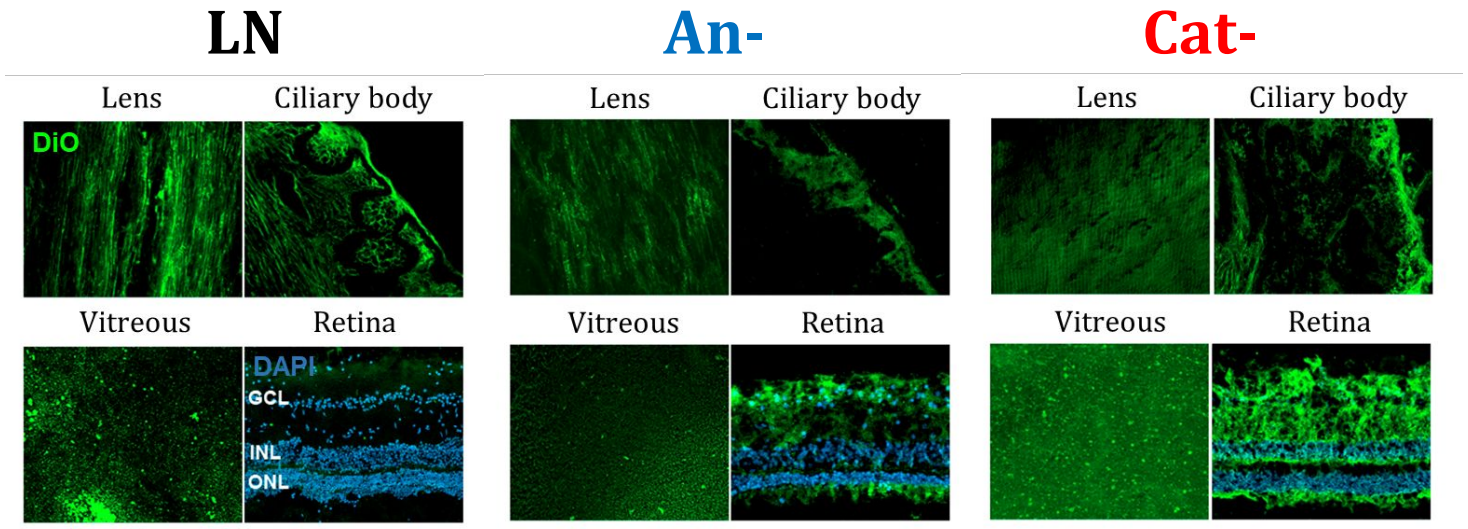
LNC injection in porcine eyes

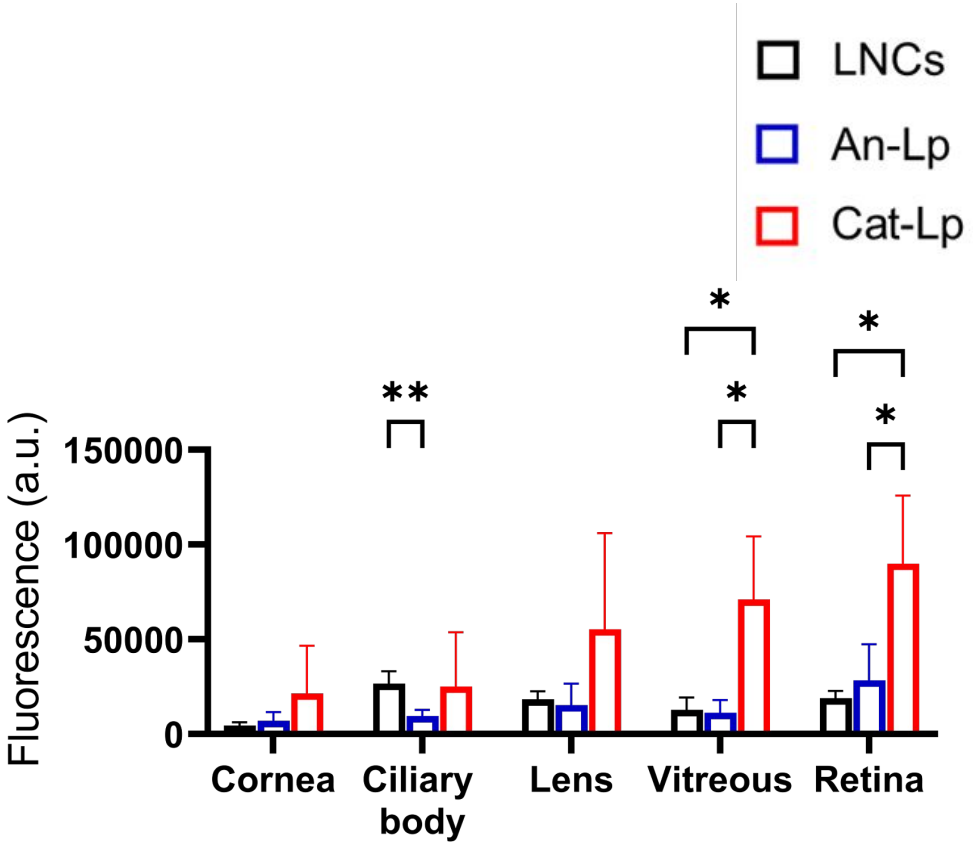




DiO

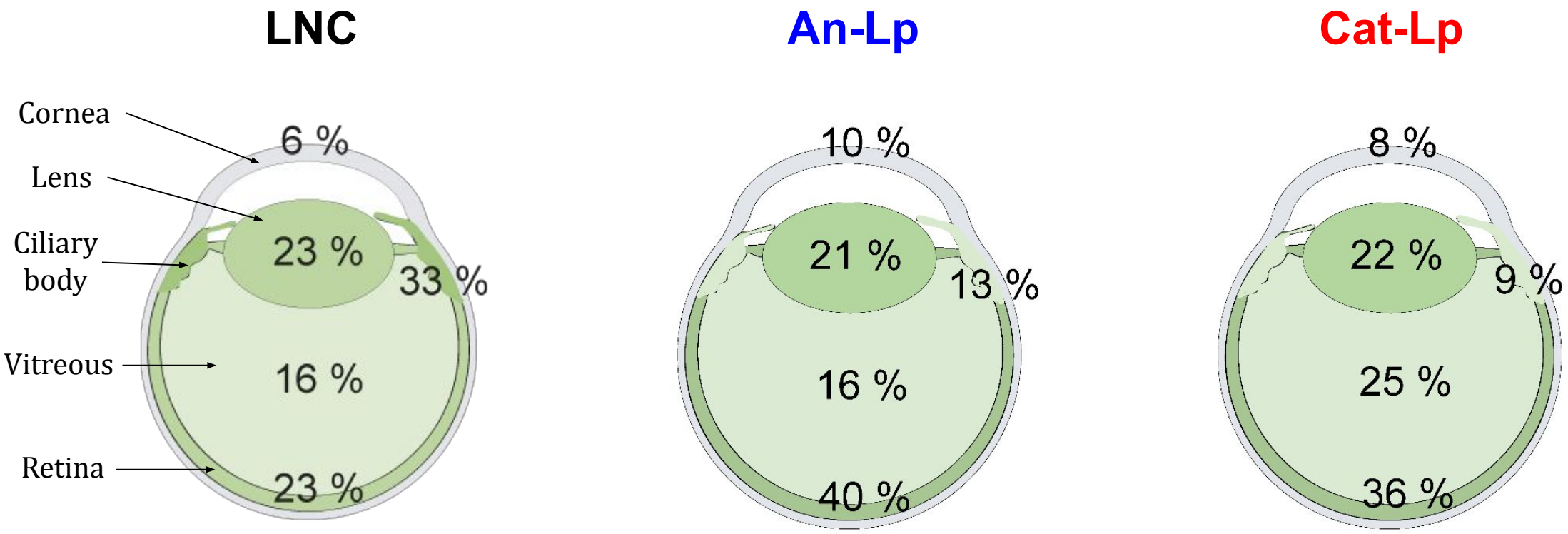
Histological analysis





Mean ± SD, n = 5-6,
* $p < 0.05$, ** $p < 0.01$

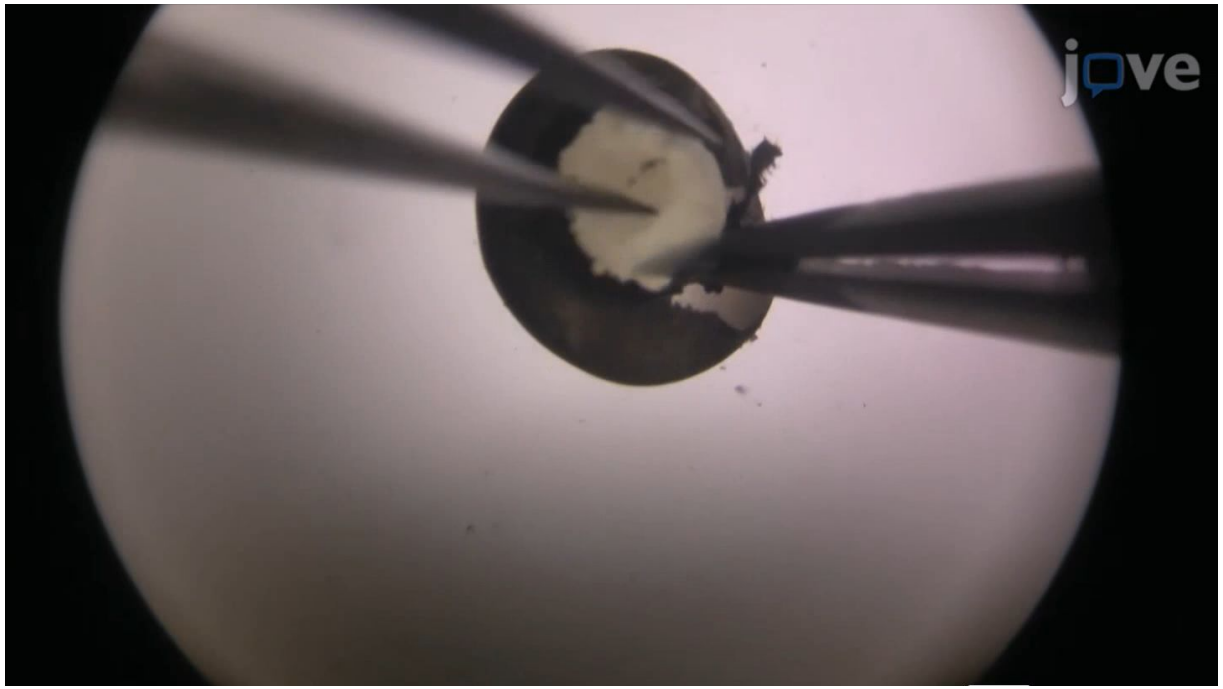
Relative bio-distribution



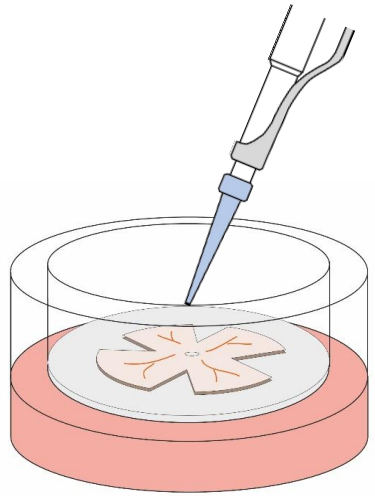
Retinal cultures derived from two mouse models

- Wild-type mice: retinal cytotoxicity analysis
- *rd1* mouse model: impaired PDE6 and cGMP accumulation. cGMP analogues (CN03 and CN04) can delay photoreceptor cell death.

Organotypic retinal explant cultures



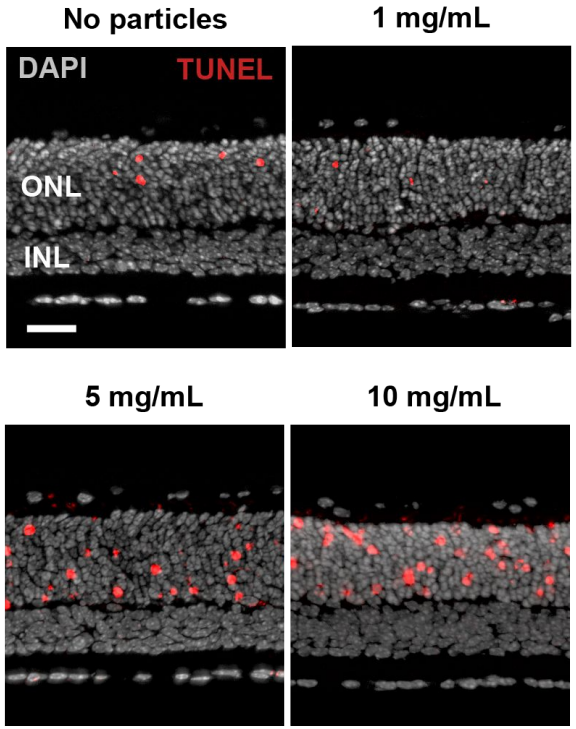
Belhadj et al. *Journal of Visualized Experiments*, 2020. DOI: 10.3791/61868-v

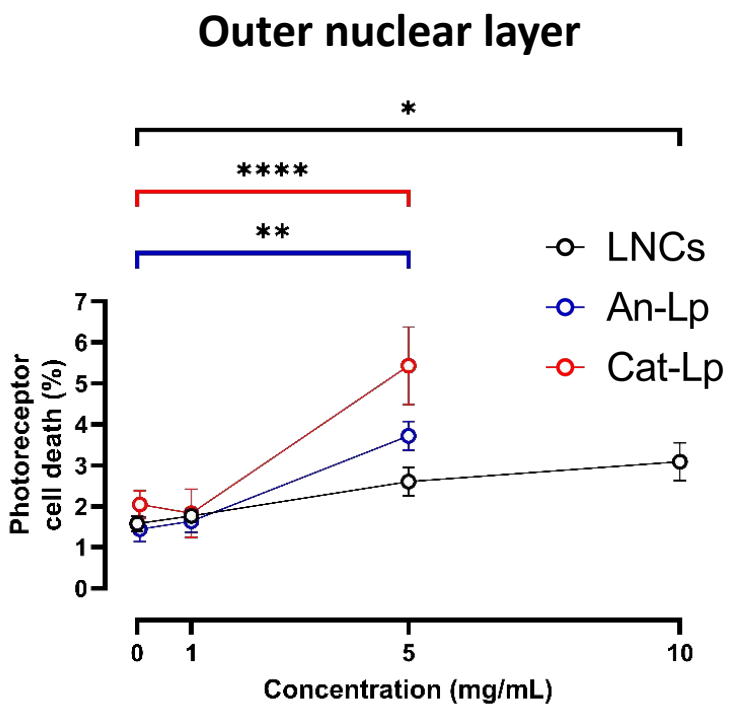


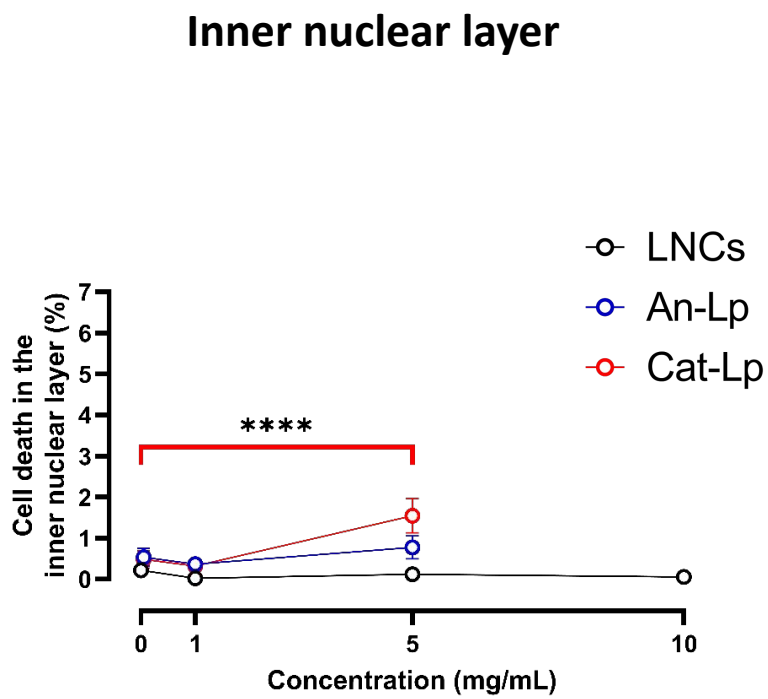
Nanoparticles added from vitreous side

Culture on a Transwell insert in well-plate

Retinal cytotoxicity

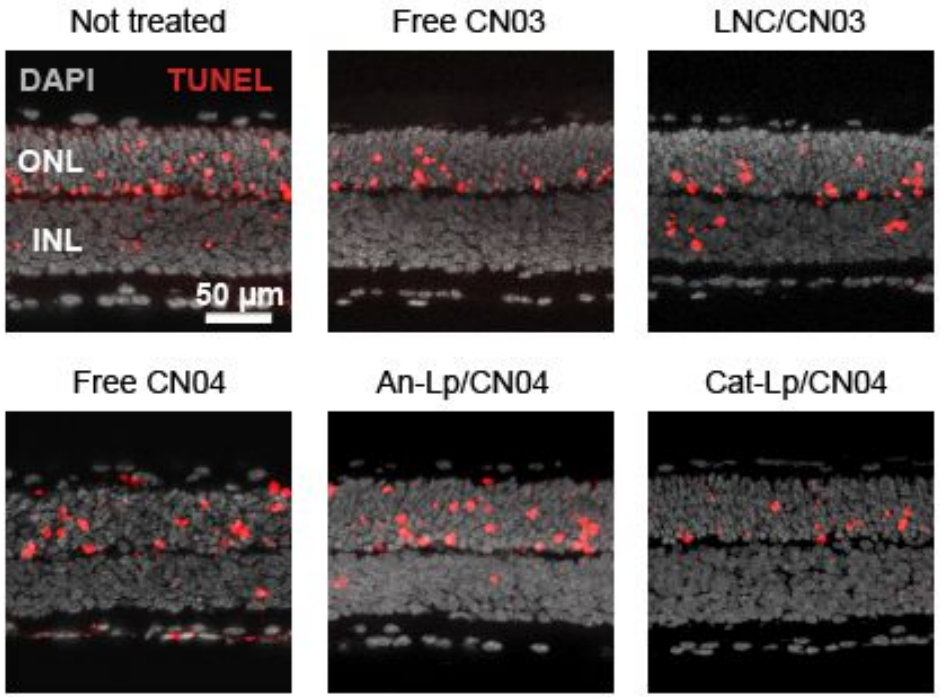


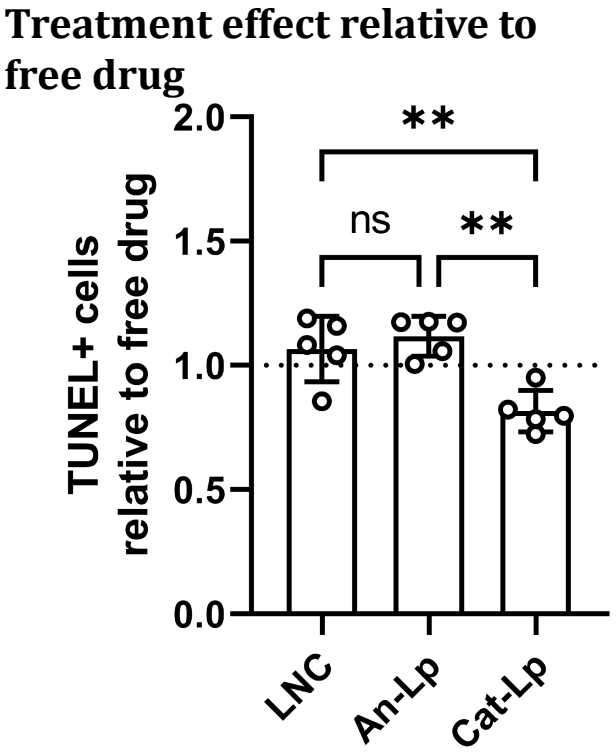




Mean ± SD, n = 4-5, * $p < 0.05$, ** $p < 0.01$, **** $p < 0.0001$

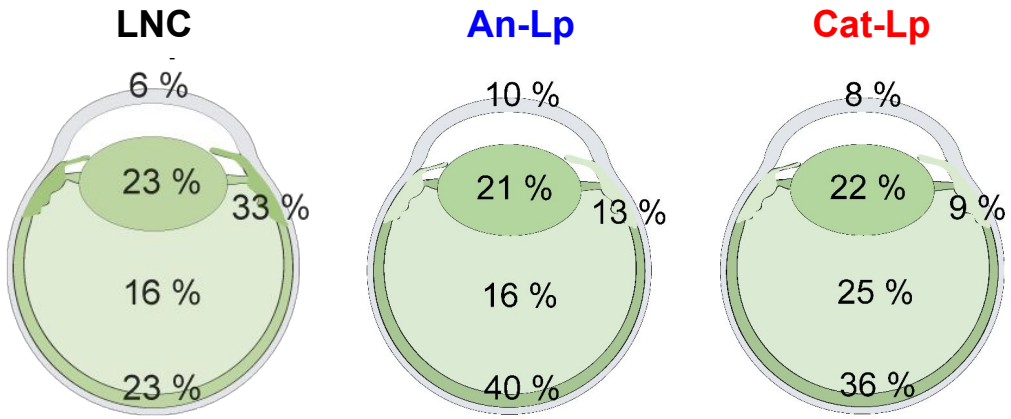
Treatment of retinal cultures derived from the *rd1* mouse model





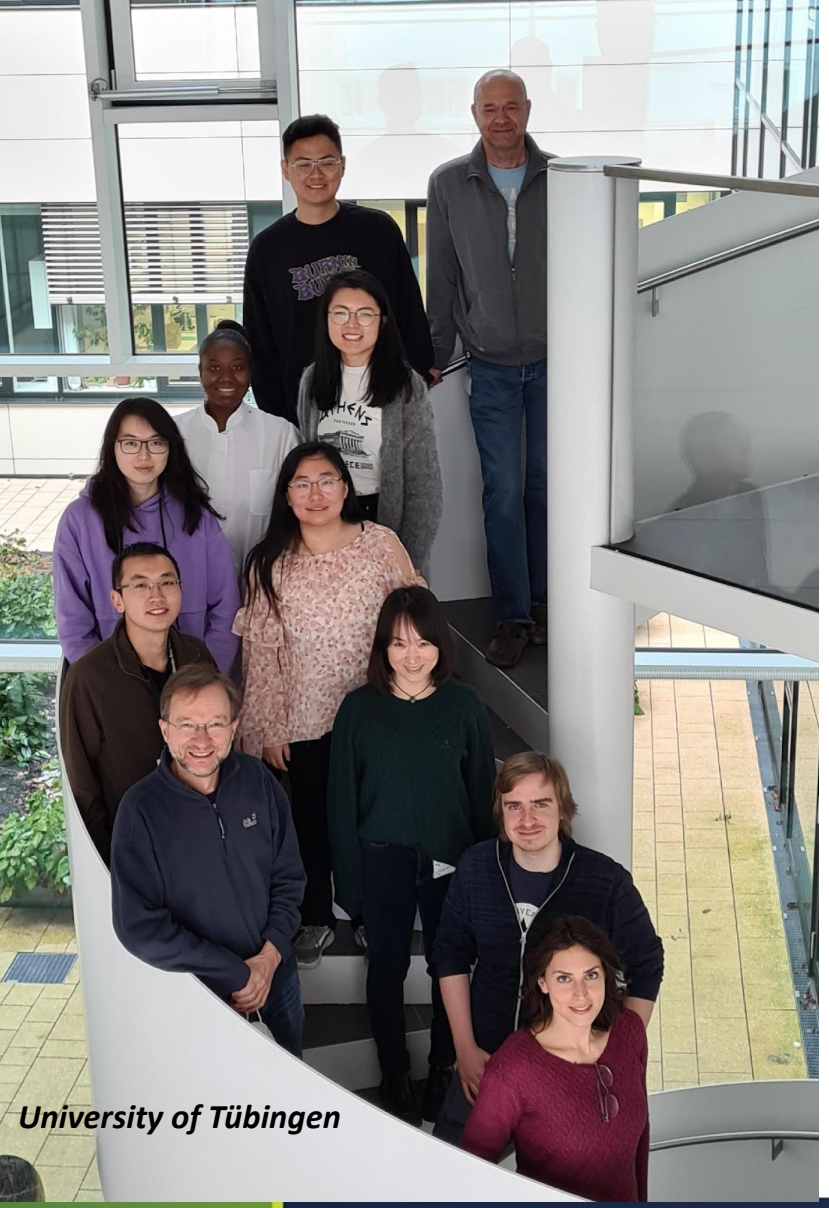
Conclusion

Bio-distribution



In vitro retinal cultures

	Retinal cytotoxicity	Treatment effect
LNC	Outer retina: low Inner retina: low	No improvement over free drug
An-Lp	Outer retina: high Inner retina: low	No improvement over free drug
Cat-Lp	Outer retina: very high Inner retina: high	Particle-mediated delivery



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Publications

G. Christensen et al., *Pharmaceutics*, 2021

Urimi et al., *International Journal of Pharmaceutics*, 2021

Vighi et al., *Proceedings of the National Academy of Sciences (PNAS)*, 2018

DFG Deutsche Forschungsgemeinschaft

Baden-Württemberg Stiftung