Sustained heme-albumin release as a potential therapy for dry age-related macular degeneration

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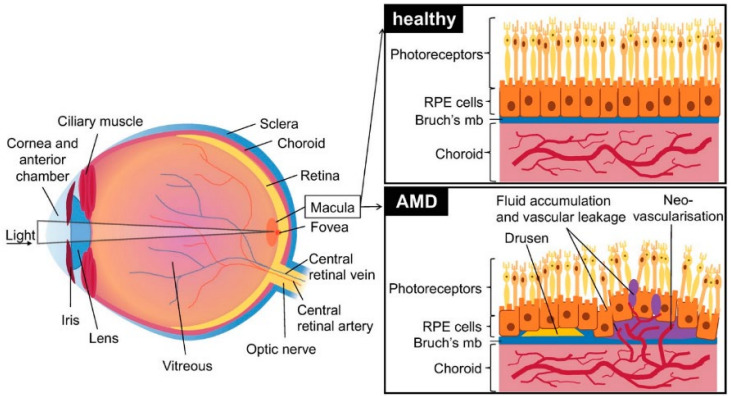
NEXT-GENERATION DELIVERY INNOVATIONS

AMD Pathogenesis

- Age-related macular degeneration (AMD) is the leading cause of vision loss in adults >65
- Retina is an oxidative stress hotspot
  Reactive oxygen species (ROS) accumulation → retinal pigment epithelium atrophy
- Two stages:

Dry AMD:
Drusen accumulation, geographic atrophy
Complement inhibitors (Syfovre, Izervay)

Wet AMD:
VEGF-driven neovascularization
VEGF inhibitors



Desai, Eye, 2022; Rastoin, Int J Mol Sci, 2020

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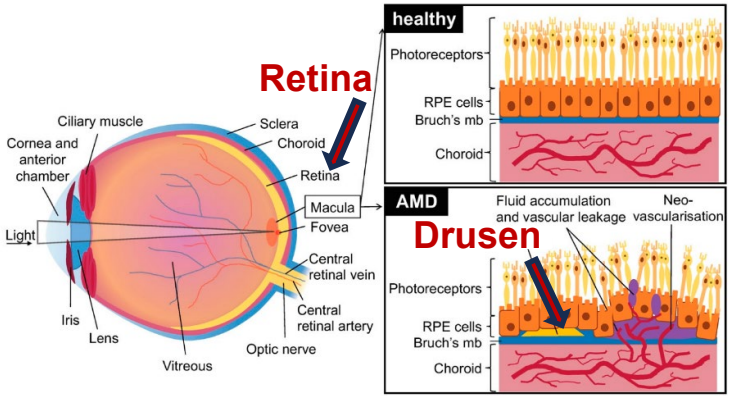


Desai, Eye, 2022; Rastoin, Int J Mol Sci, 2020

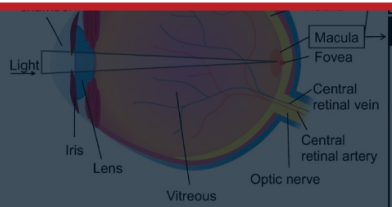
AMD Pathogenesis

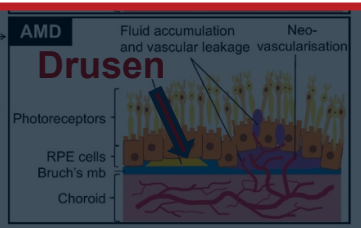
CURRENT TREATMENT SHORTCOMINGS:

- Limited therapeutic efficacy
- Short therapeutic half-life → frequent injections → reduced patient adherence

PROPOSED SOLUTION:

- Upstream disease modification
- Sustained release → reduce injections → improve patient adherence & visual outcomes

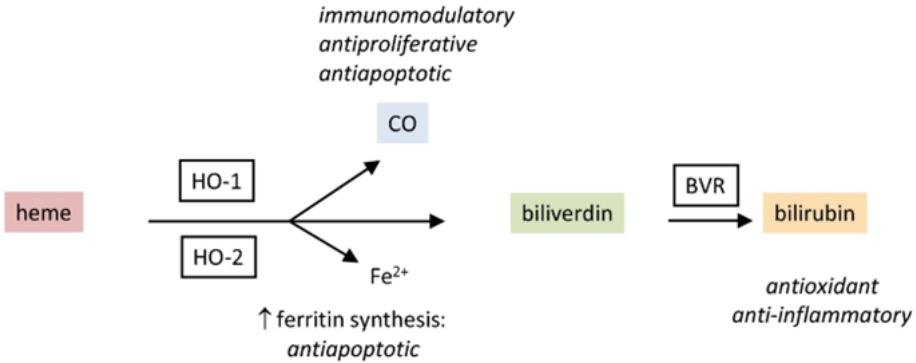




Goal - Induce Heme Oxygenase-1 (HO-1) and Decrease ROS

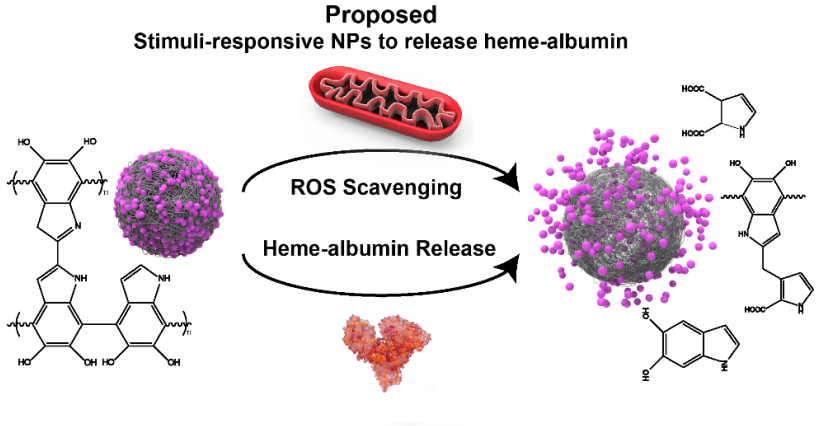
Heme-Albumin

Shortcomings of heme
mitigated with albumin complex



Polydopamine nanoparticles (PDA NPs)

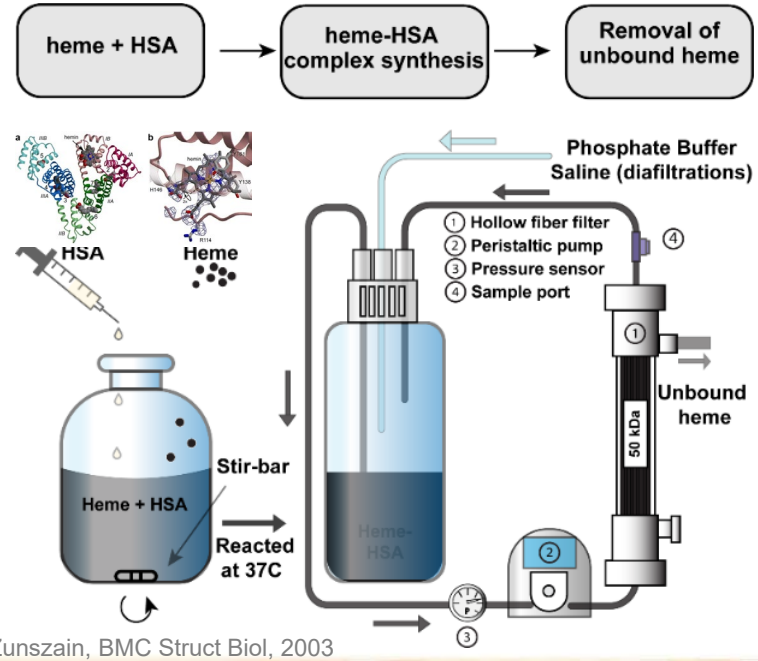
Redox-responsive → biodegradable → sustained release



Jiang, Nanoscale, 2020; Allyn, Biomater Sci, 2022

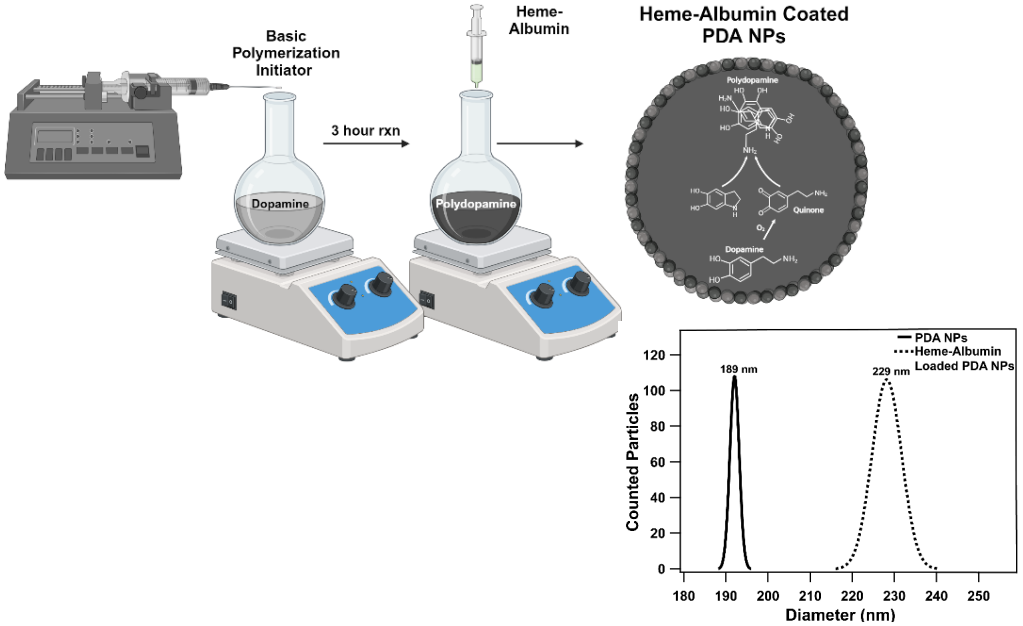
Preparation & Characterization

Heme-Albumin



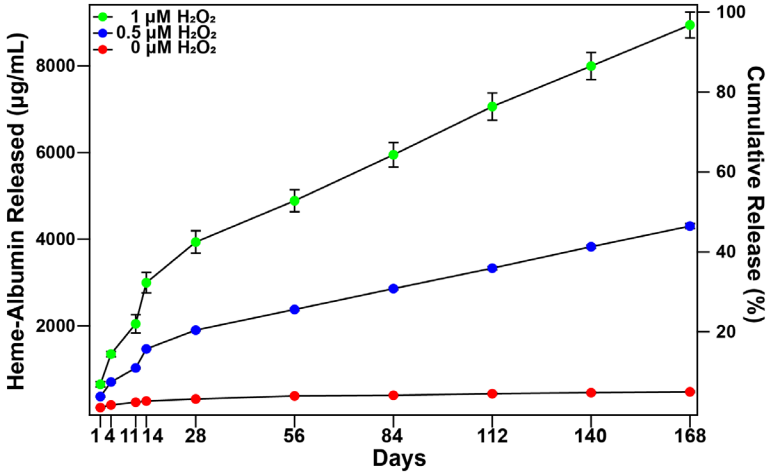
Zunszain, BMC Struct Biol, 2003

PDA NPs



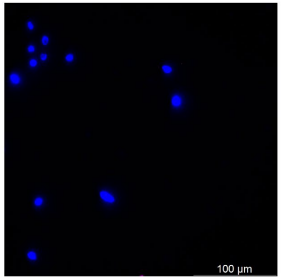
Allyn, Biomater Sci, 2022

In Vitro Release and Uptake

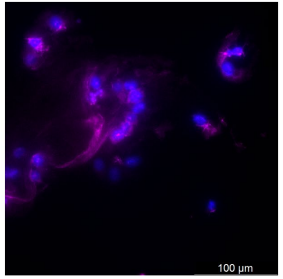


Release increased with ROS (H_2O_2)

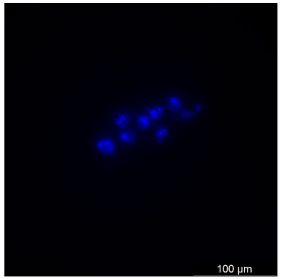
ARPE-19 (human retinal pigment epithelial cell) uptake of heme-albumin and loaded PDA NPs



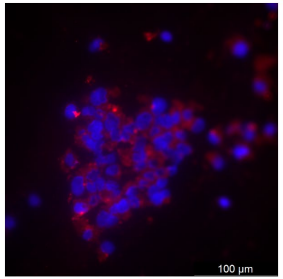
2 mg/mL Heme-Albumin



2 mg/mL Cy7-Heme-Albumin



100 µg/mL Heme-Albumin loaded PDA NPs



100 µg/mL Heme-Albumin loaded 594-PDA NPs

Allyn, Biomater Sci, 2022

In Vivo Study Design

Adult C57BL/6J mice (8-12 weeks, both sexes)

1 µL intravitreal injections of heme-albumin or PDA NPs

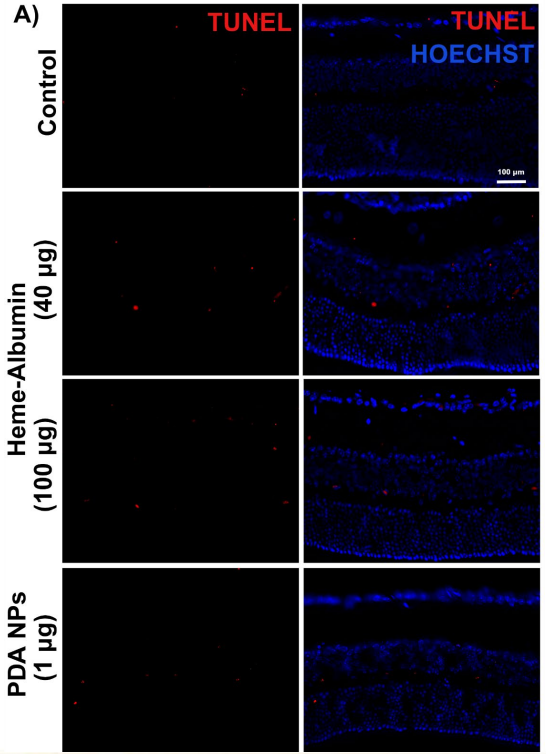
IHC and SD-OCT (optical coherence tomography)

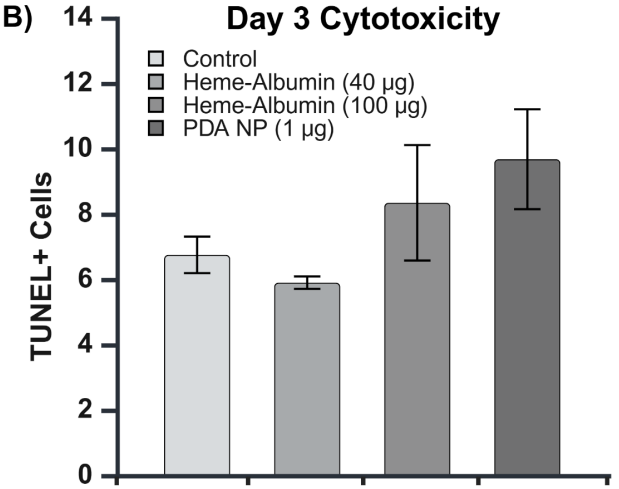
Treatment Group	Dose	Timepoints—day(s) (D)	Sample size (n), respectively
Heme-albumin (OS)	Low Dose (LD; 40 µg)	1, 3, 14	7, 3, 10
	High Dose (HD; 100 µg)	1, 3, 14	7, 3, 10
PDA NPs (OS)	Single dose (1 µg)	1, 3, 7	7, 3, 3
Control (OD)	Vehicle (PBS) / untreated	1, 3, 7, 14	7, 3, 3, 10

Cytotoxicity Screening

TUNEL (560 nm) stain for retinal cell death with nuclear counterstain HOECHST (390 nm)

No significant differences at D1 (not shown) or **D3** (shown) for doses tested





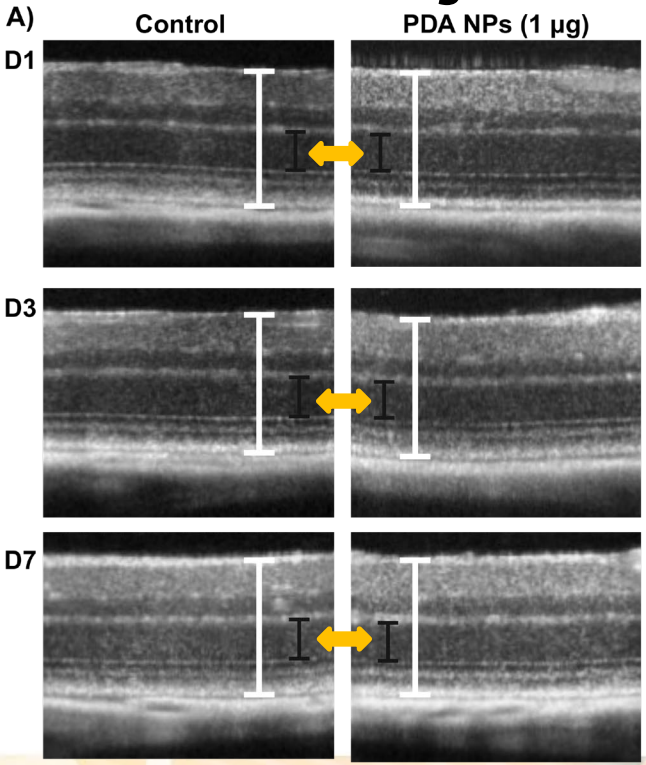
- Two-way ANOVA followed by Tukey's HSD test comparison
- n=3 for all groups (3 slides per animal, 3 micrographs per tissue section)

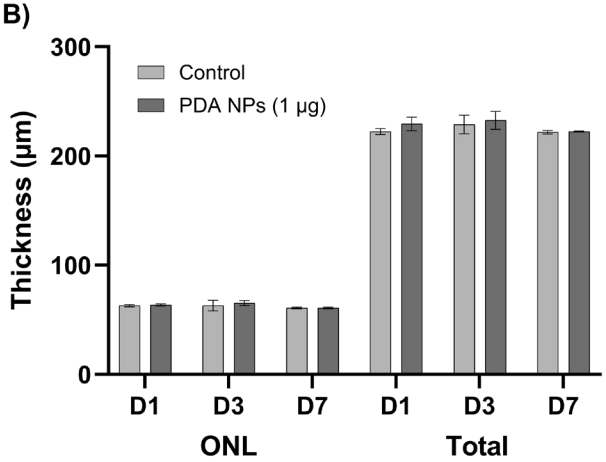
SD-OCT after PDA NP Injection

Outer nuclear layer (ONL) and total retinal thickness D1, D3, D7

<u>No significant differences</u> for ONL or total retinal thickness at any time point

White brackets = total retina
Black brackets = ONL





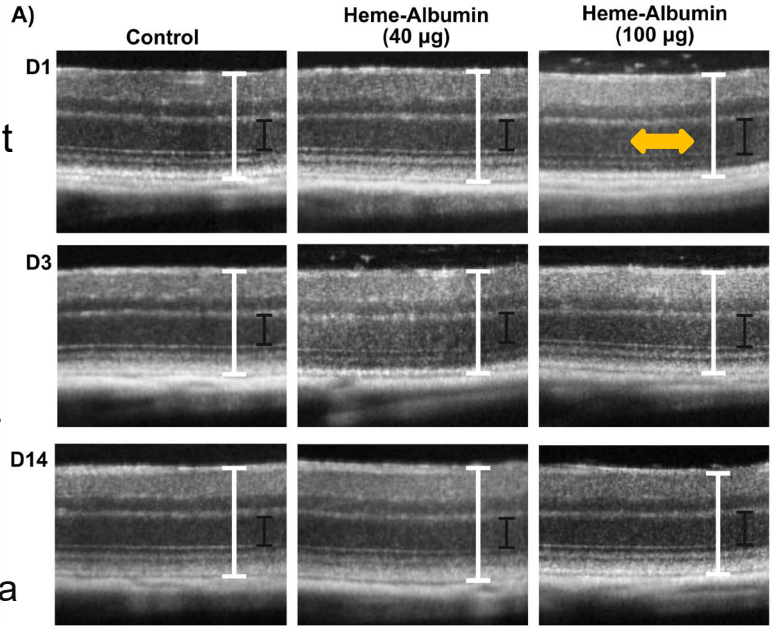
- Radial B-scans averaged for 3-5 measurements approximately 0.35 mm from optic nerve head (ONH)
- Two-way ANOVA followed by Tukey's HSD test
- n=3 per group

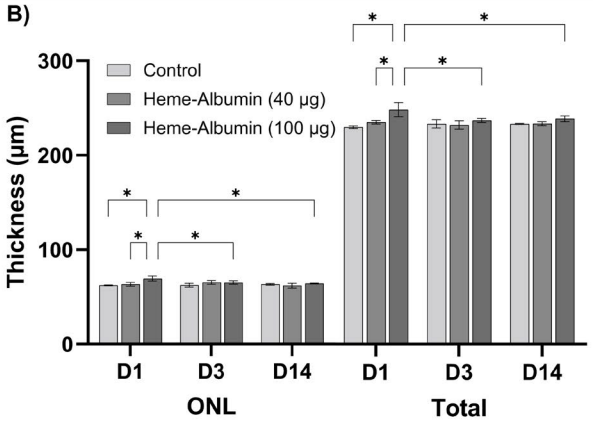
SD-OCT after Heme-Albumin Injection

Outer nuclear layer (ONL) and total retinal thickness at D1, D3, D14

At D1, high dose heme-albumin groups had significantly increased ONL and total retinal thickness, which resolved by D3

White brackets = total retina
Black brackets = ONL





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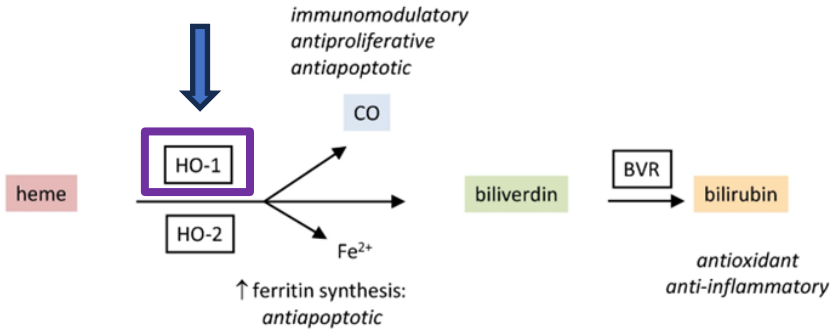
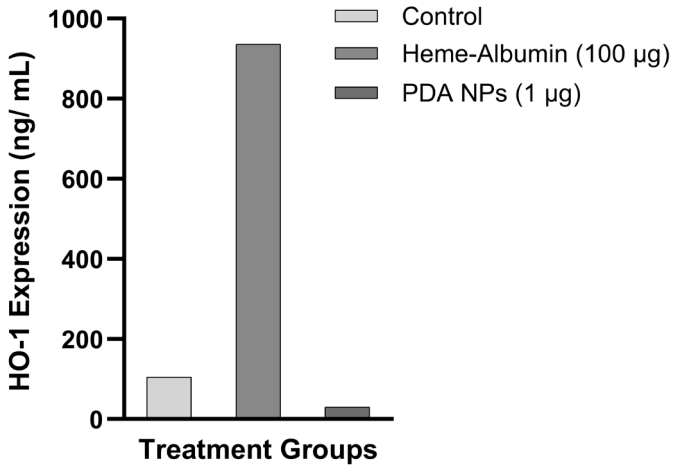
Treatment-Induced HO-1 Expression

D1 expression of HO-1 (ELISA) from pooled (n=3) mouse retinal tissue

Heme-albumin induced ~10-fold higher HO-1 expression compared to control



Allyn, Biomater Sci, 2022



- Single pooled sample (n=3) per group (n=3-4)

Summary

Treatments tolerated *in vivo*: heme-albumin and PDA NPs were well tolerated with minimal retinal apoptosis and maintained retinal layer integrity

Therapeutic activity without toxicity: heme-albumin effectively induced HO-1, a cytoprotective enzyme, without compromising retinal integrity

Conclusions: heme-albumin and PDA NPs demonstrate short-term *in vivo* safety and show potential to mitigate oxidative stress and inflammation associated with early AMD pathogenesis

Ongoing work:

- Additional IHC analysis
- Treatment efficacy in a sodium iodate-induced retinal degeneration model
- PDA NP evaluation in other models

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