Dr Carole D. Thomas

Enhanced efficacy of PDT when combined with nitroglycerin ointment admnistration on xenografted Retinoblastoma in mice

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RÉTINOSTOP

Aim of the study : Two goals

1- To determine if PhotoDynamic Therapy (PDT) associated with NitroGlycerin ointment (NG : Rectogesic®) is able to induce a major cellular death on an human line of retinoblastoma

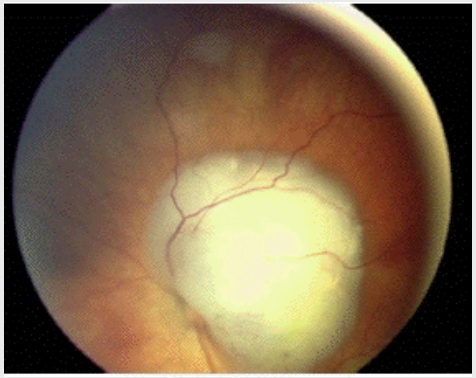
2- To determine if extracellular sodium MRI follow-up is able to give rapid information about tumor cells destruction

RETINOBLASTOMA

- Most common intraocular tumour in children
- Malignant tumour of the retina
- Uni- or bilateral involvement
- Rare : 1 in 15-20,000 births; 50-60 cases / year in France
- Excellent survival in the most privileged countries
- Frequent relapses and poor visual prognosis

Current treatments

- Laser and cryotherapy
- Chemotherapy (systemic and local)
- Depending on tumour location and size: enucleation



Problem of toxicity

- hearing problems: deafness
- Mutagenesis (secondary cancer)
- Formation of a scar that impairs vision

The development of alternative treatment protocols, like PDT, using non mutagenic drugs is an important challenge

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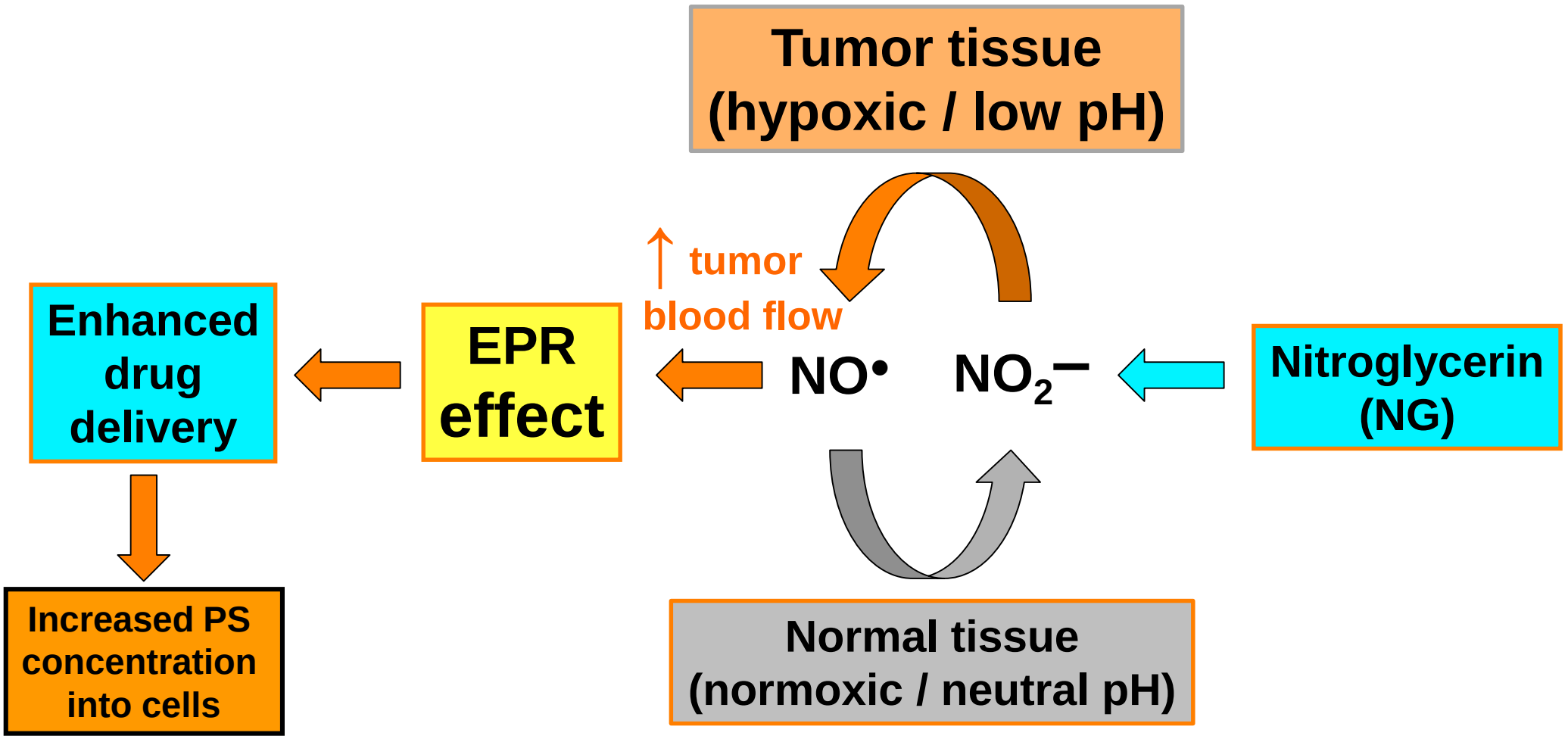
Nitroglycerin is known to dilate vessels and to enhance the permeability and retention of macromolecules in solid tumors [1]



EPR: Enhanced Permeability and Retention

From : Maeda H.
Proc. Jpn Acad Ser 88,53-71, 2012

[1] Seki T. *et al*., Cancer Science, 2009, 12, 2426-30

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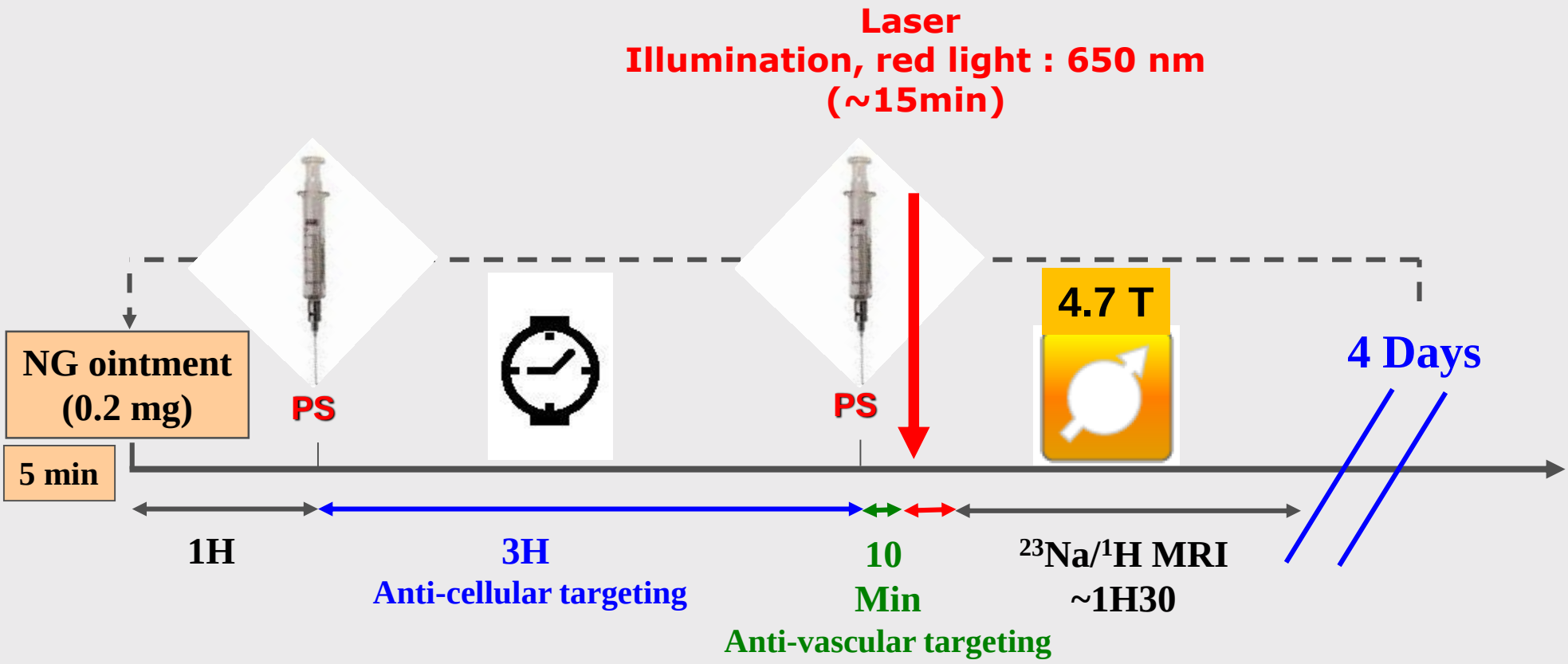
TREATMENT PROTOCOL



At the end of the follow-up (day 14) : histology

- ✓ **H&E**
- ✓ **Apoptosis detection**

METHODS

Mice : ♀ swiss « nude » mice

Tumors : Human retinoblastoma xenografted on the flank

: the less responsive tumor line of all tested in our lab

Nitroglycerin (Rectogesic®) : 0.2 mg ointment was apply on the skin during 5 min

Photosensitizer (PS) : glycoconjugated porphyrin derivative 100 µl i.v. injected (retro-orbital sinus)

For PDT and MRI experiments :

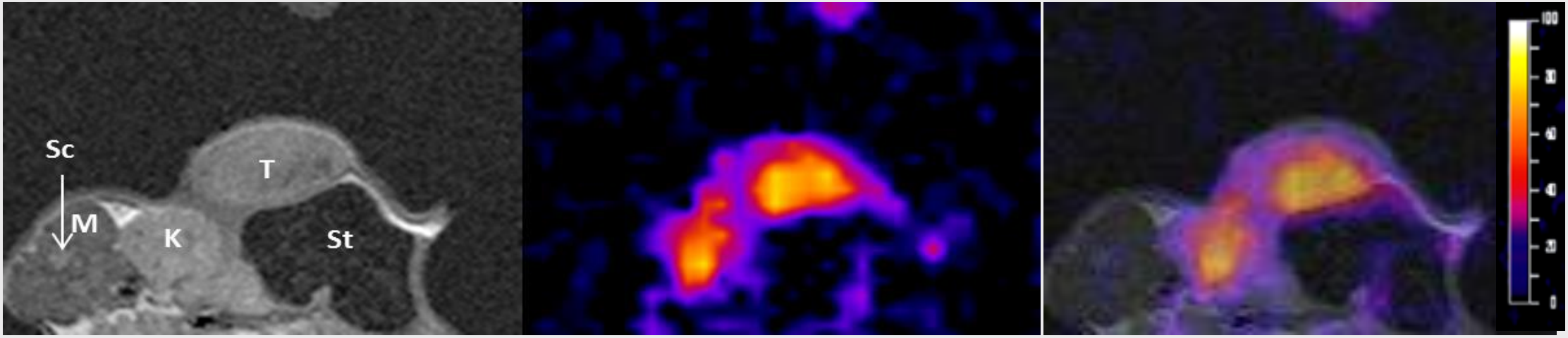
- **mice anesthetized with isofluran (1.5 -2%),**
- **mice temperature being kept constant (warm water carpet)**

RESULTS : PROTON AND SODIUM MRI

Functional imaging modality : Sodium MRI directly monitors variations of sodium concentrations in a non-invasive way

Variations of Na content reflected variations of the extra-cellular space

Vascular damages and necrosis or apoptosis decrease cell density and increase the local Na content



Bystander effect : Process generated by the initial dead cells on the light pathway
damages = apoptosis continuing beyond PDT limits (light penetration)
in time and space

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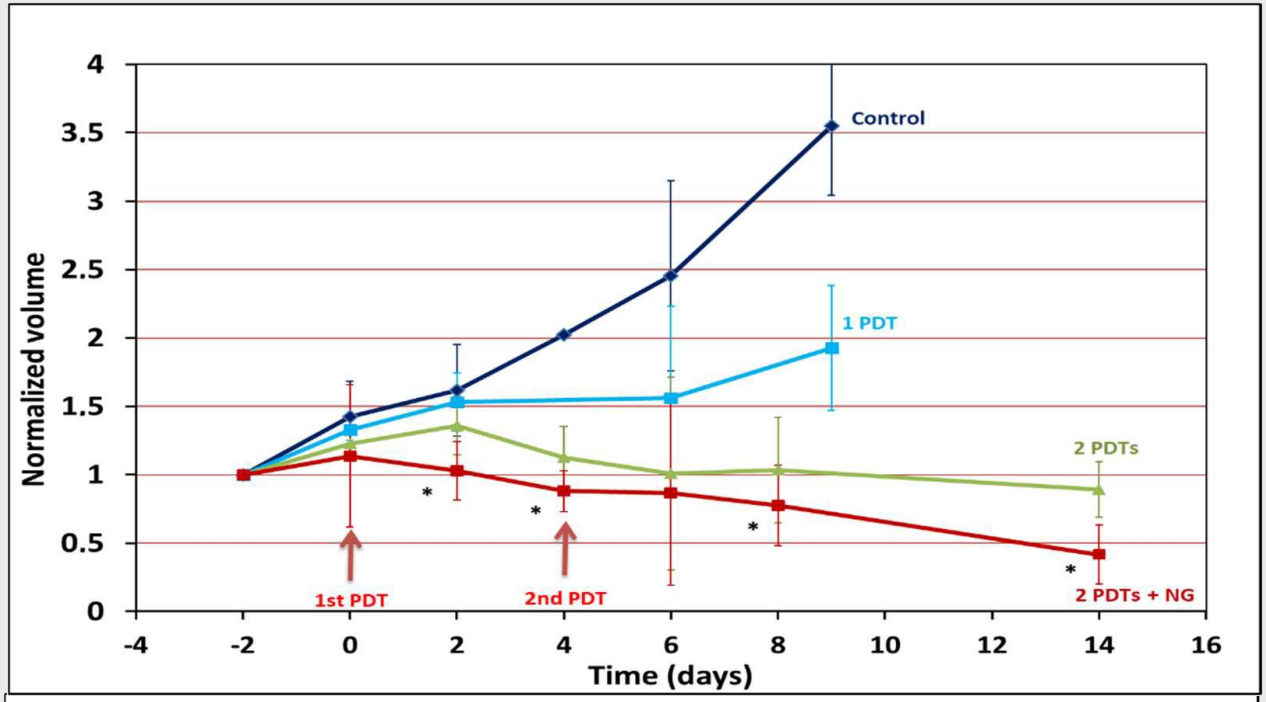
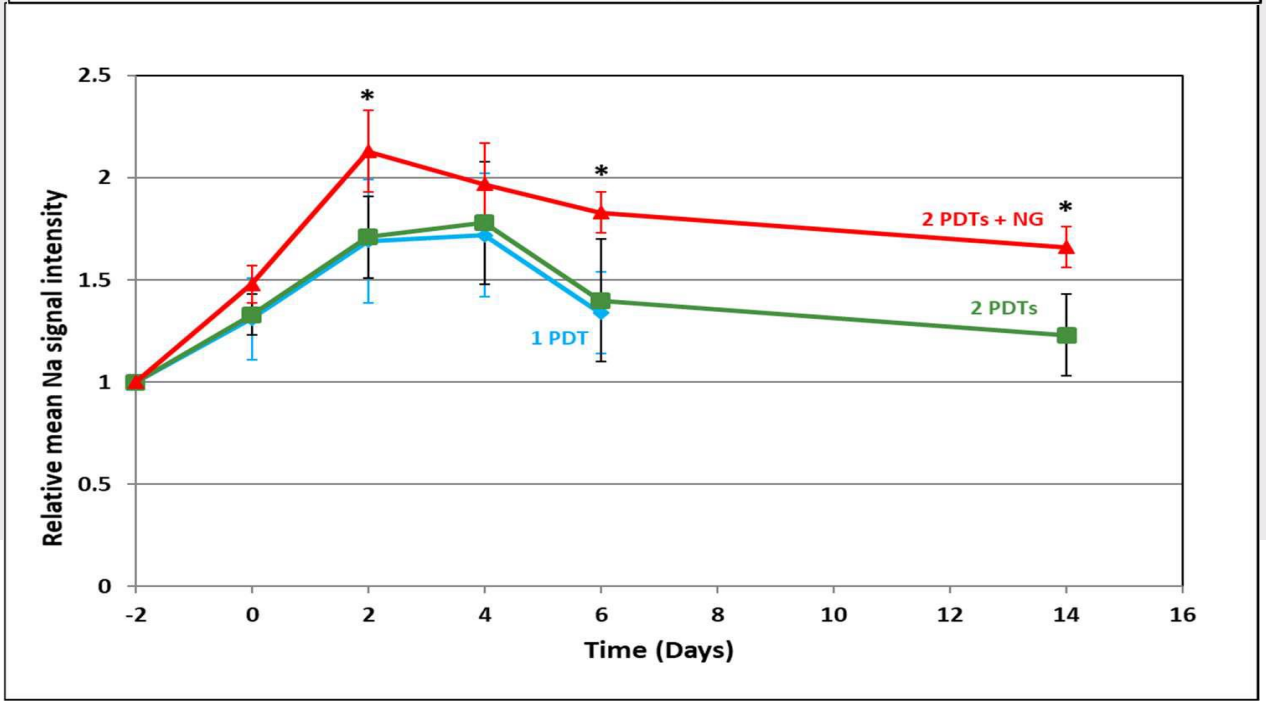
RESULTS





✓ **PDT (anti-vascular + anti-cellular) hindered the tumoral progression and stopped it**

✓ **NG increased the tumor response to PDT, triggering off the bystander effect**

✓ **This effect was found even after the first PDT treatment**

NG allowed to reach the treatment result parameters similar to those of the most responsive tumor line tested in our lab

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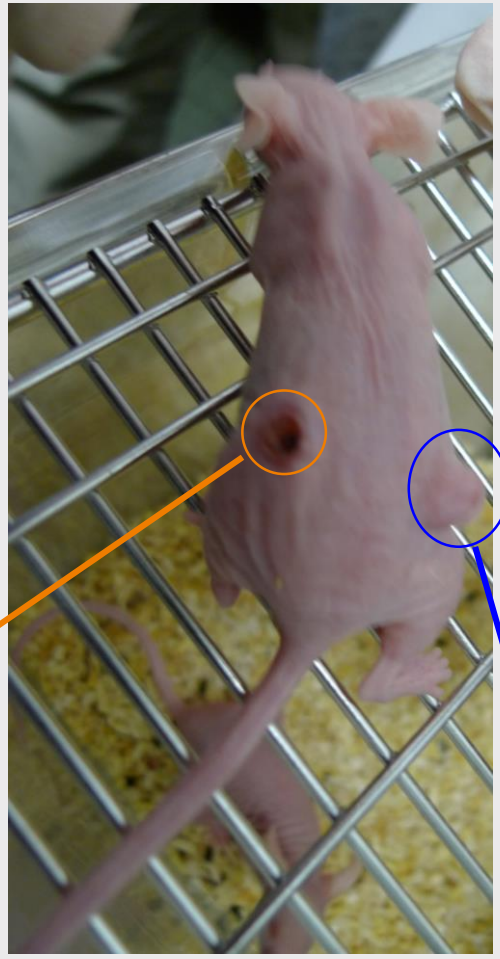
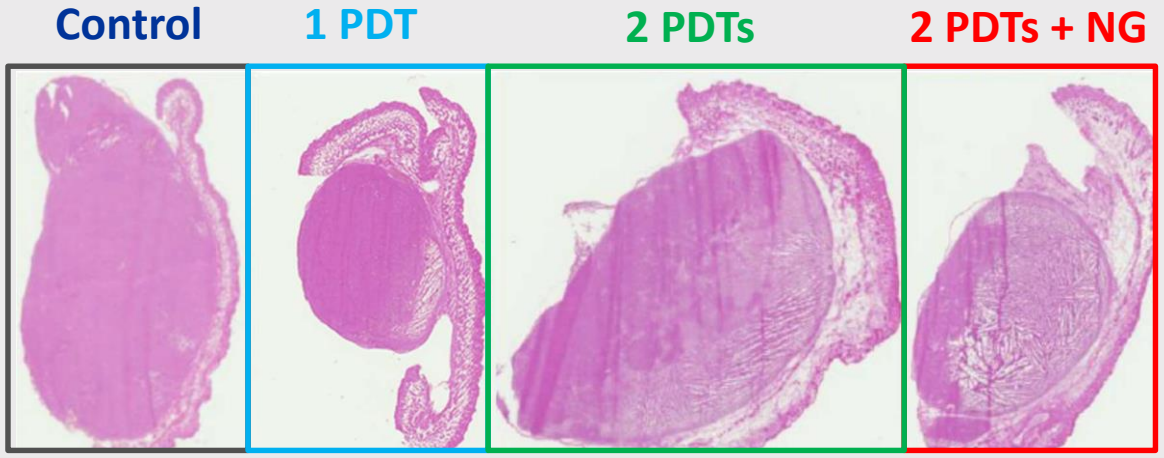
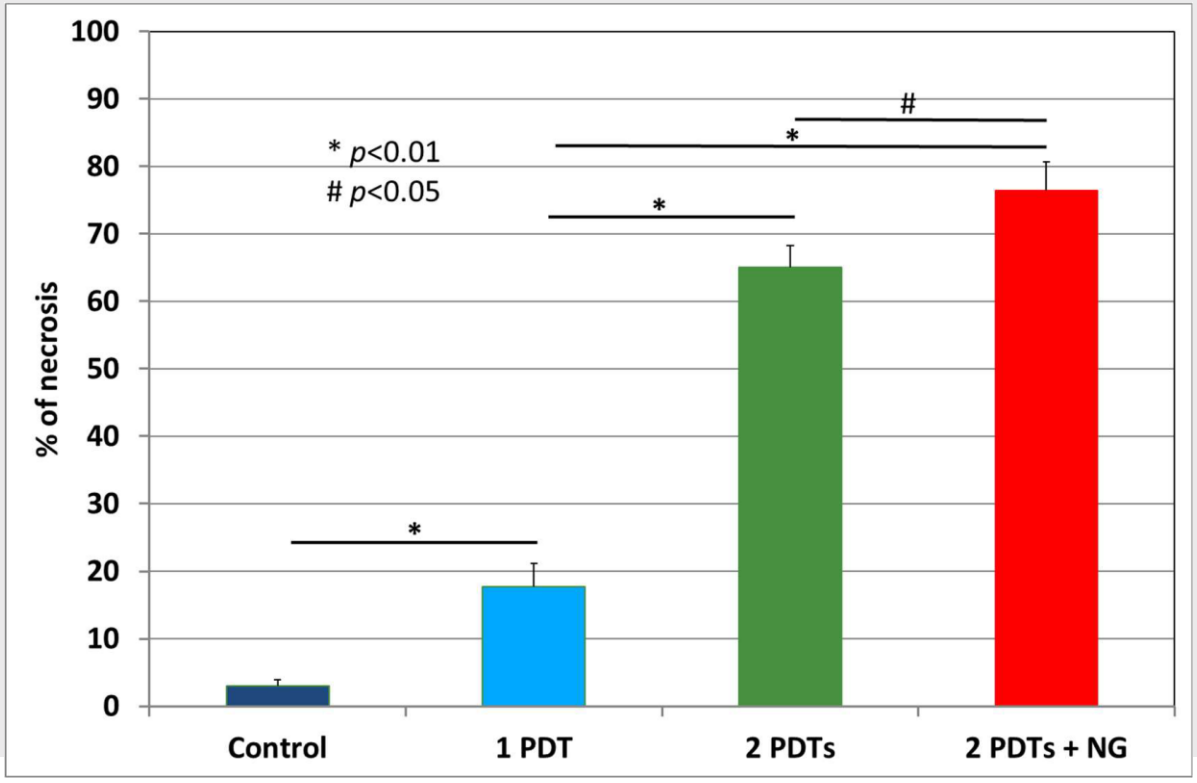
RESULTS



The installed necrosis was confirmed by histology





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CONCLUSIONS

- ✓ **PDT is effective in treating retinoblastomas**
- ✓ **NG ointment + PDT increases the treatment efficiency for tumor lines that are less responsive to PDT treatment.**
- ✓ **NG increases the PDT efficacy by enhancing the intratumor concentration of PS inducing a more significant production of ROSs on the illuminated region increasing thus the propagation of cellular death signalling deeper into the tumor (bystander effect).**

The use of NG is an easy and inexpensive way to improve the efficacy of PDT, especially for tumors that respond poorly to PDT alone.

→ many important advantages for potential clinical use.

Thanks to my colleagues

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Thank you for your attention

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