In Vitro and In Vivo Efficacy of Nitric Oxide-Releasing Antiviral Therapeutic Agents

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Disclosures

- This presentation contains forward-looking statements including, but not limited to, statements related to pharmaceutical development of nitric oxide-based product candidates and future prospects. Forward-looking statements are subject to a number of risks and uncertainties that could cause actual results to differ materially from our expectations. These forward-looking statements speak only as of the date of this presentation, and Novan disclaims any intent or obligation to update these forward-looking statements, except as expressly required by law.

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Genital and Perianal Warts: Human Papillomaviruses

- Most common sexually transmitted infection
- Approximately 14 million people become infected each year
- >500,000 people in the United States are actively infected
- No currently approved HPV treatments with a direct anti-viral mechanism of action
- Topical and ablative therapies are largely ineffective for long-term wart eradication.
  - Average recurrence rates ranging from 30% to 70% within the first 6 months

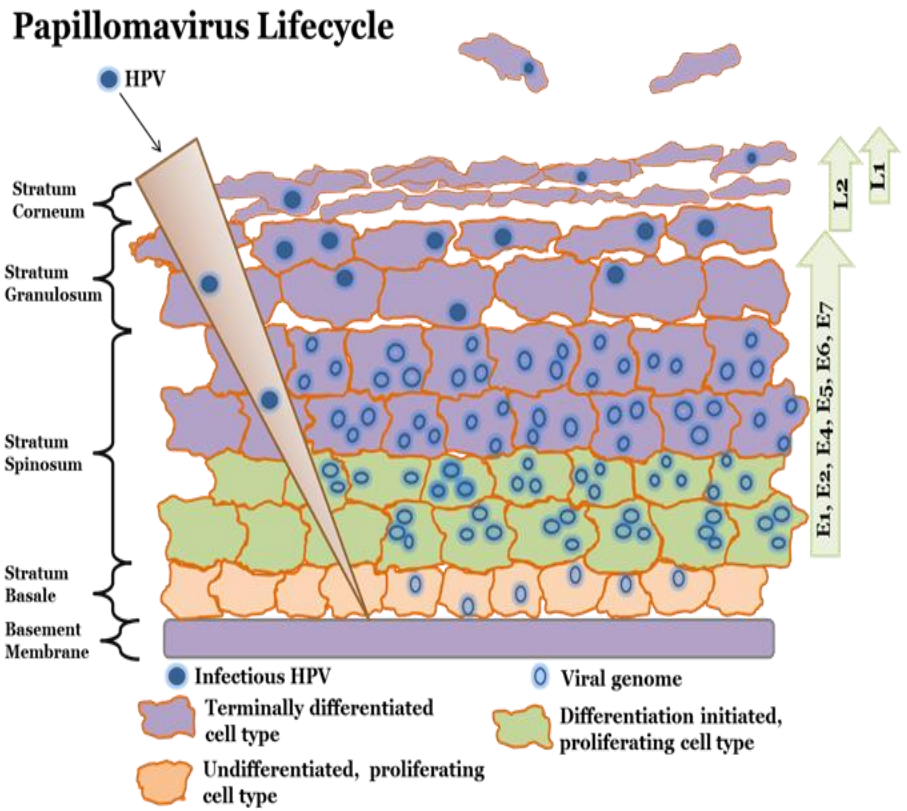

Image from Brendle, 2014 *Curr Probl Dermatol*

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Two Fundamental Mechanisms of Action of Nitric Oxide

Broad Spectrum Antimicrobial

Modulator of Inflammation

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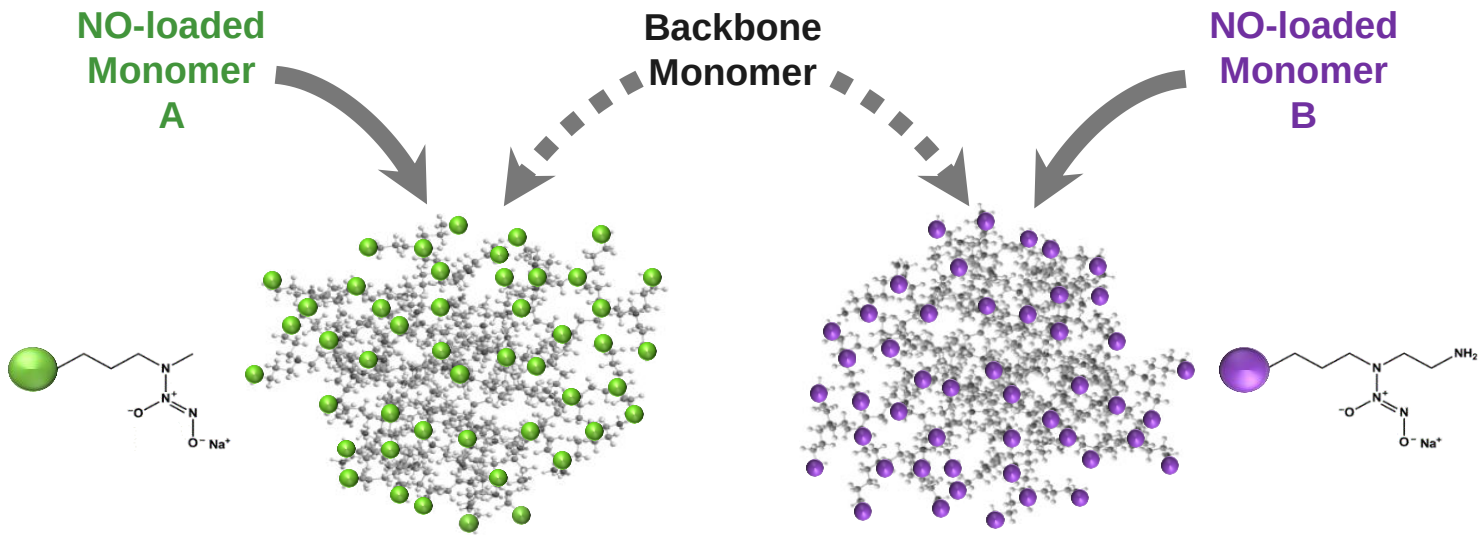
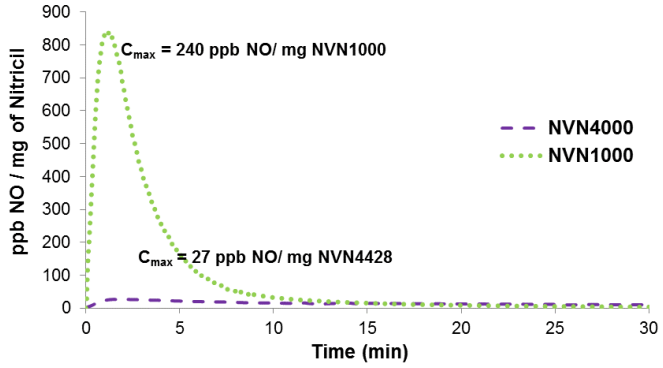
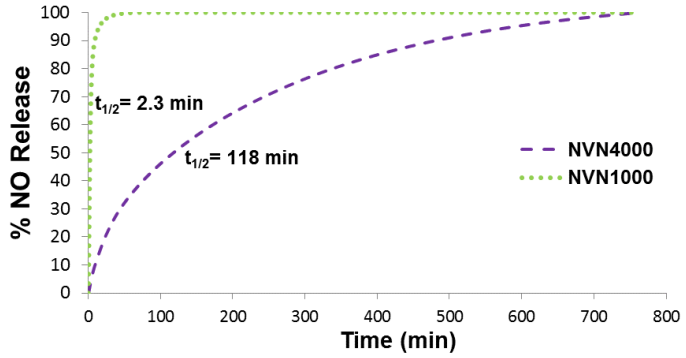
Nitricil: Lead Candidate NCEs

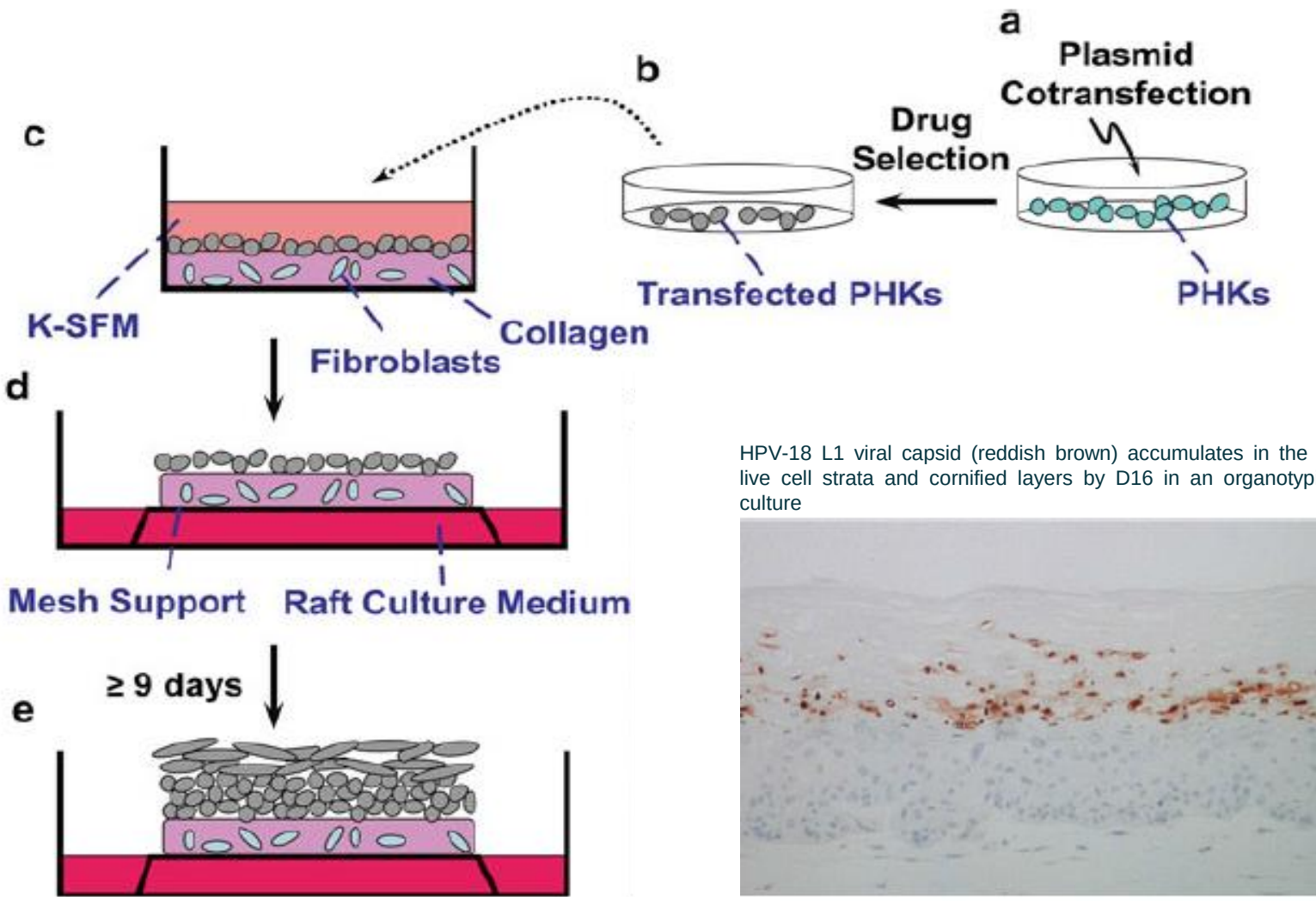


In vitro nitric oxide release profiles at pH 7.4





HPV-18 Infected Organotypic Epithelial Raft Culture Model



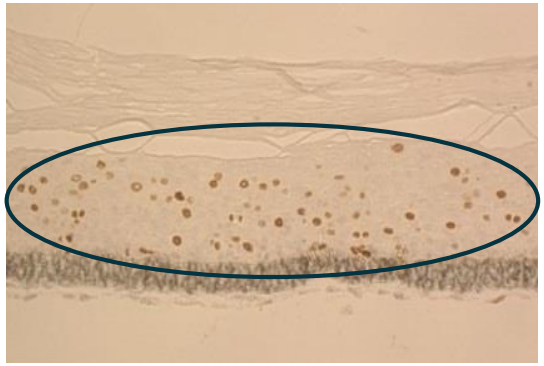
HPV-18 L1 viral capsid (reddish brown) accumulates in the upper live cell strata and cornified layers by D16 in an organotypic raft culture

Image adapted from Wang, 2015 *Methods Mol Bio*

Nitric Oxide Inhibition of DNA Replication

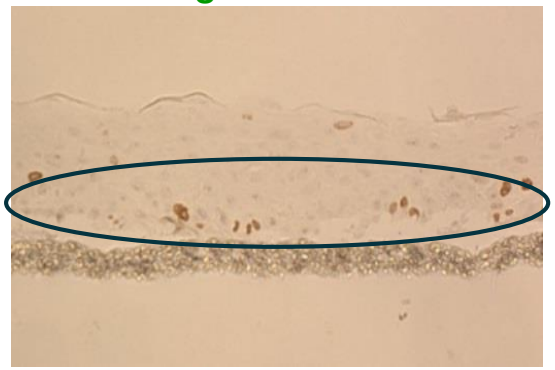
BrdU Stain, mitotic index for rapidly dividing nuclei

Untreated Control

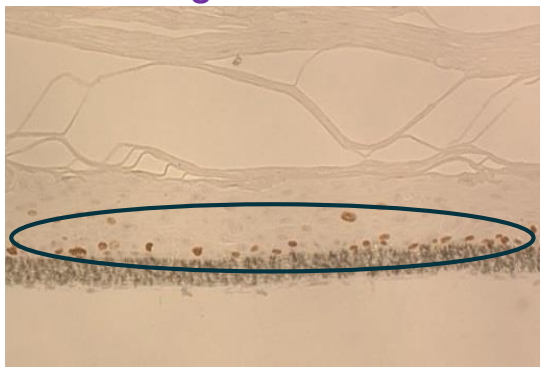


Large number of BrdU stained cells indicative of pervasive viral infection throughout epithelium

1.5 mg/mL NVN1000



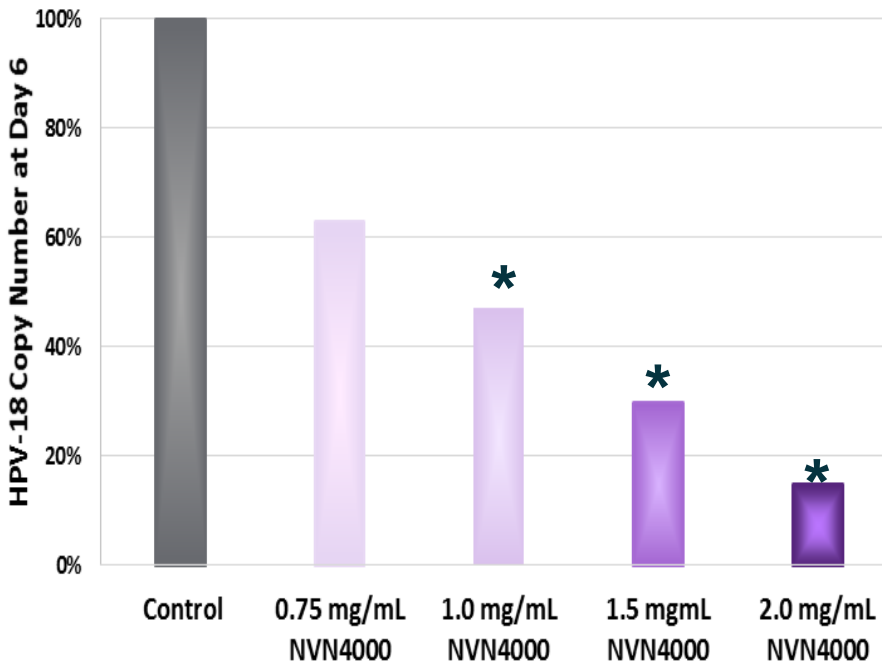
1.5 mg/mL NVN4000

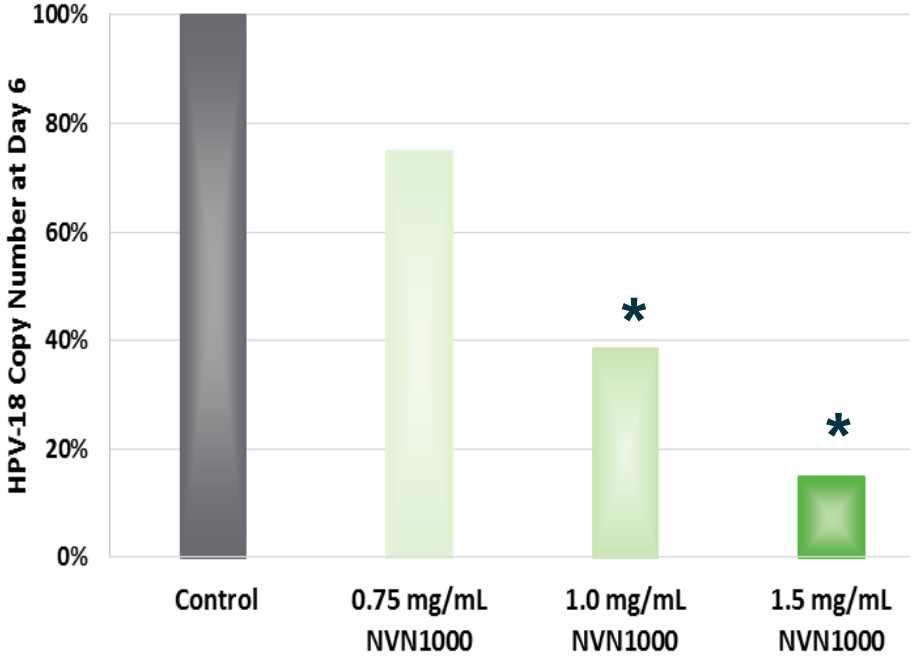


Mitotic activity present only at basal layers indicative of normal epithelium proliferation

Nitric Oxide Inhibition of Viral Replication

qPCR analysis of HPV-18 viral copy number





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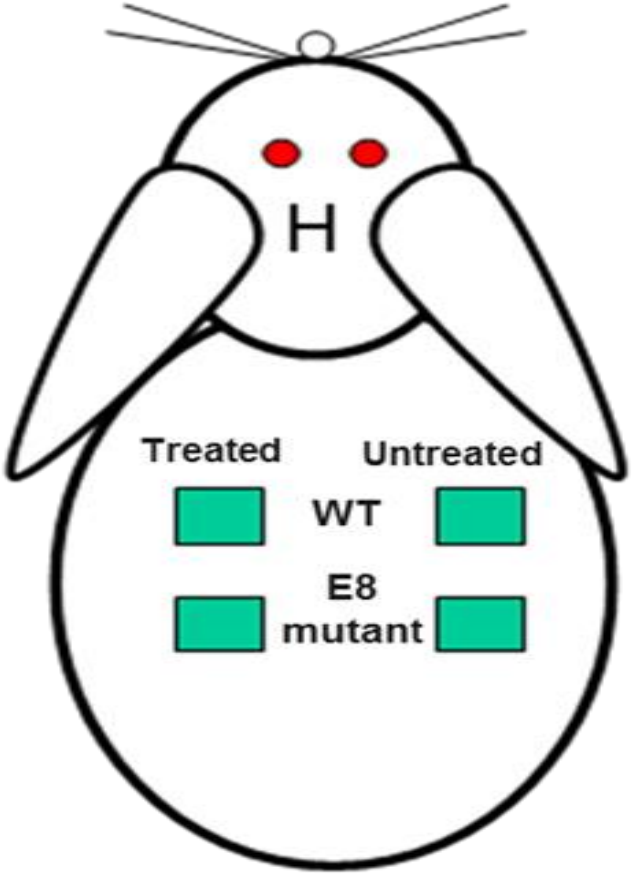
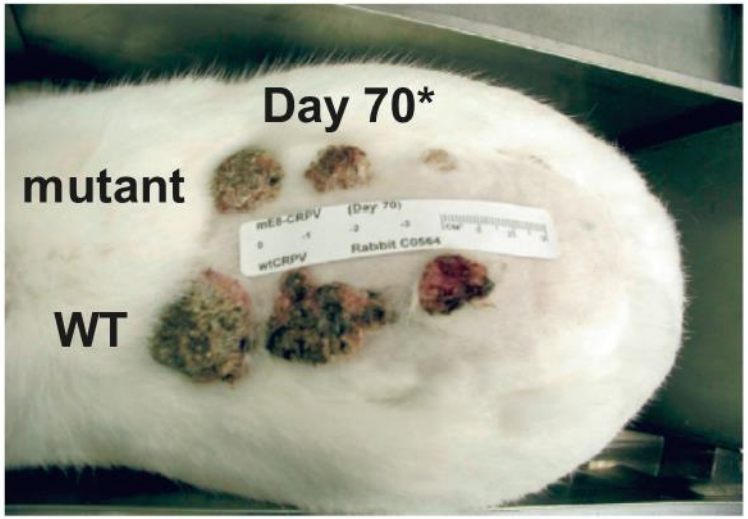
Cottontail Rabbit Papillomavirus Model





- Mutant virus results generates smaller, slower-growing papillomas thought to be more clinically similar to human papillomas.
- The E8 mutant papillomas are much lower in height and are less keratinized than those induced by WT CRPV.

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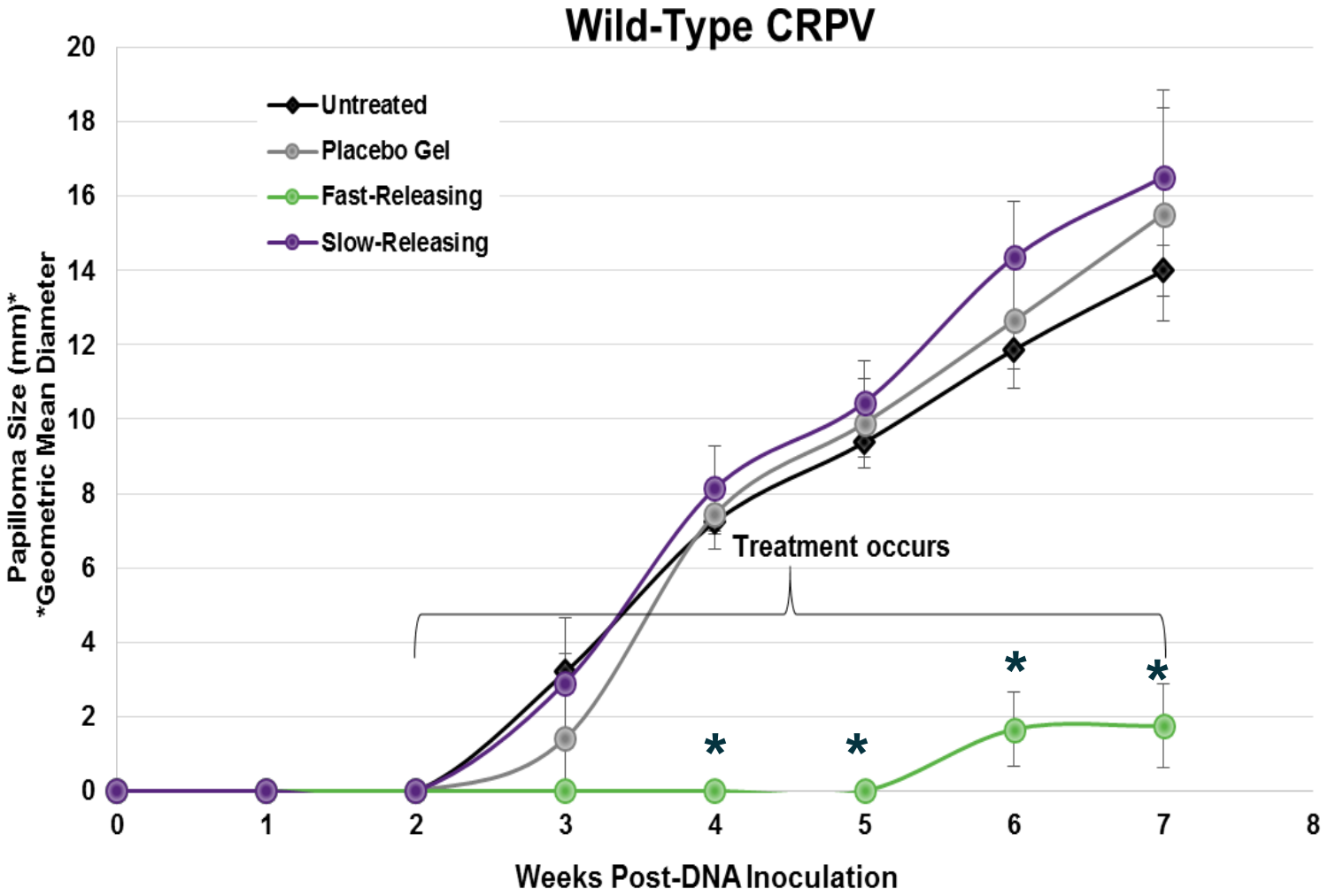
Nitric Oxide Delivery: Fast Release is Superior



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Nitric Oxide Delivery: threshold concentration necessary for depth of penetration

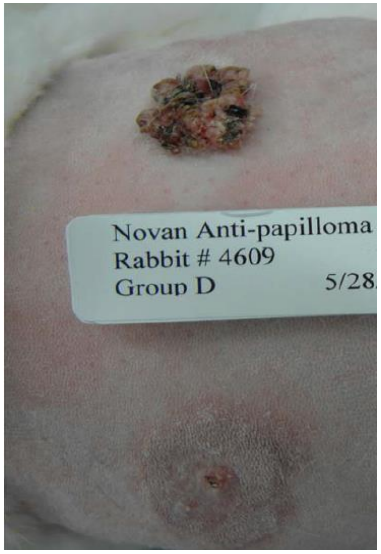
A)

Placebo Gel

B)

Slow-Releasing: SB216 Gel
1.5% NO

C)



Fast-Releasing: SB206 Gel
1.5% NO

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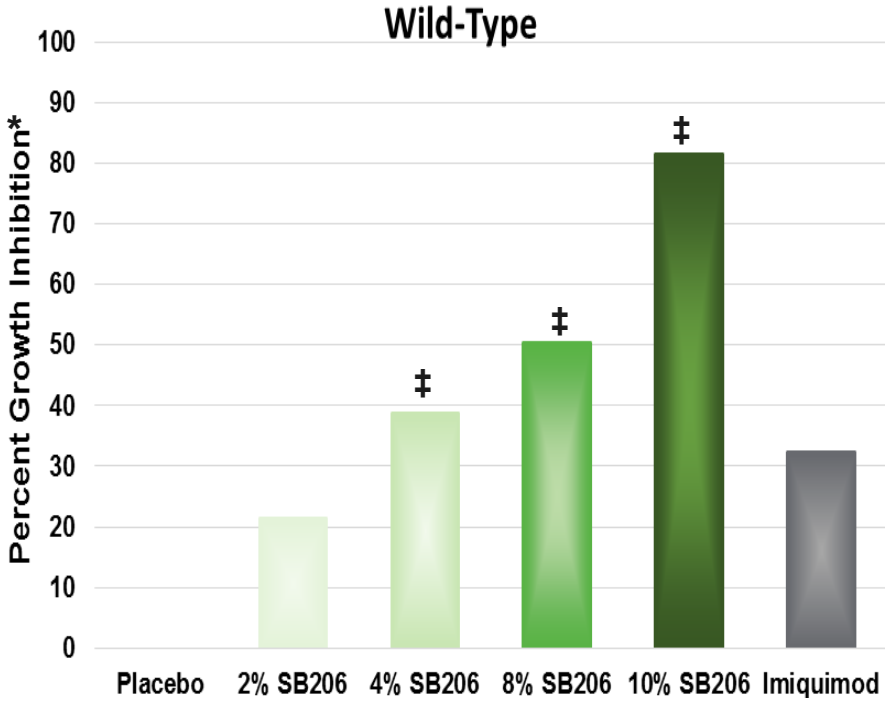
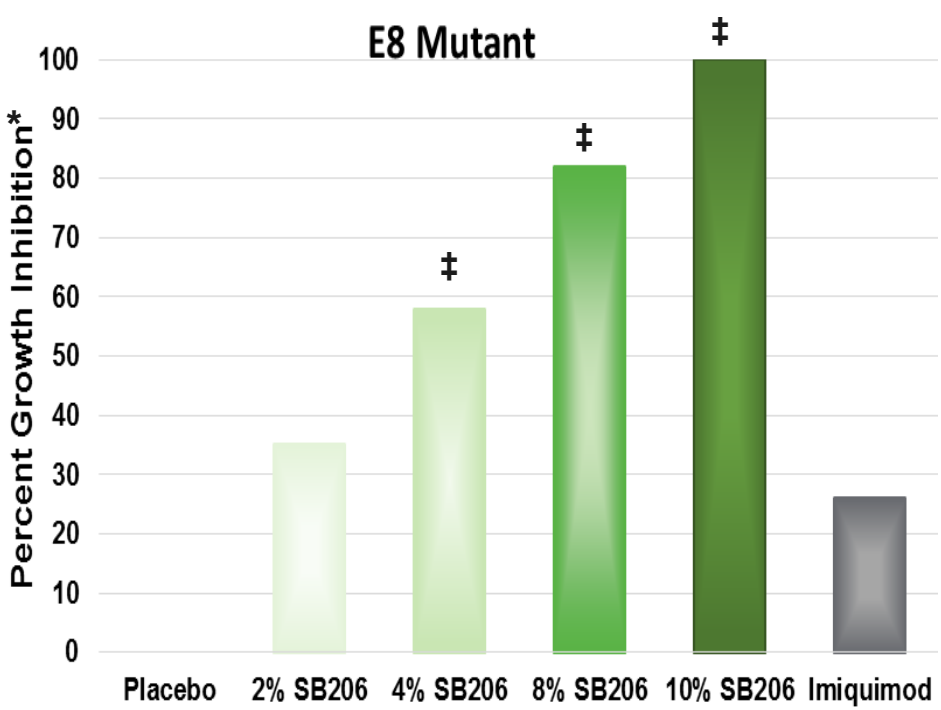
Dose-Response of SB206 Gel Treatment

The E8 mutant virus produces slower-growing and more clinically relevant papillomas than the Wild-Type virus.





*** vs. Placebo Control Following 5 Weeks of Treatment**

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Conclusions

- **Dose-dependent inhibition of HPV-18 viral replication as evidenced by both DNA copy number and BrdU immunohistochemistry.**
  - **Similar efficacy with NVN1000 or NVN4000 drug substance**
- **Dose-responsive, pharmacologic effect of SB206 Gel against papillomavirus in the Cottontail Rabbit model.**
- **Topical therapy with SB206 Gel is currently being studied in a Phase 2 EGW/PAW Clinical Trial with TLRs expected 2H 2016.**

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Acknowledgements

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Thank You

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