Nitric Oxide-Releasing Topical Therapeutic for Atopic Dermatitis

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- 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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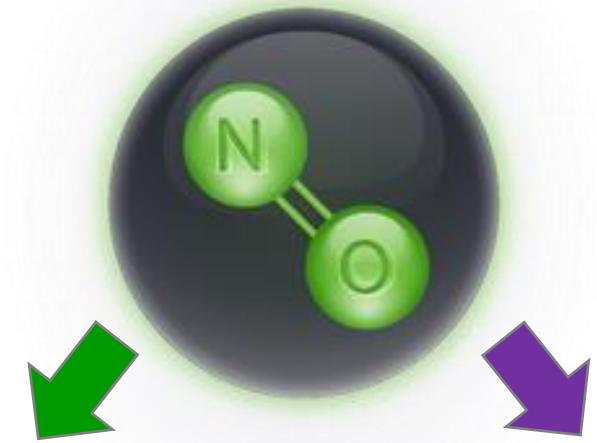
Two Fundamental Mechanisms of Action of Nitric Oxide



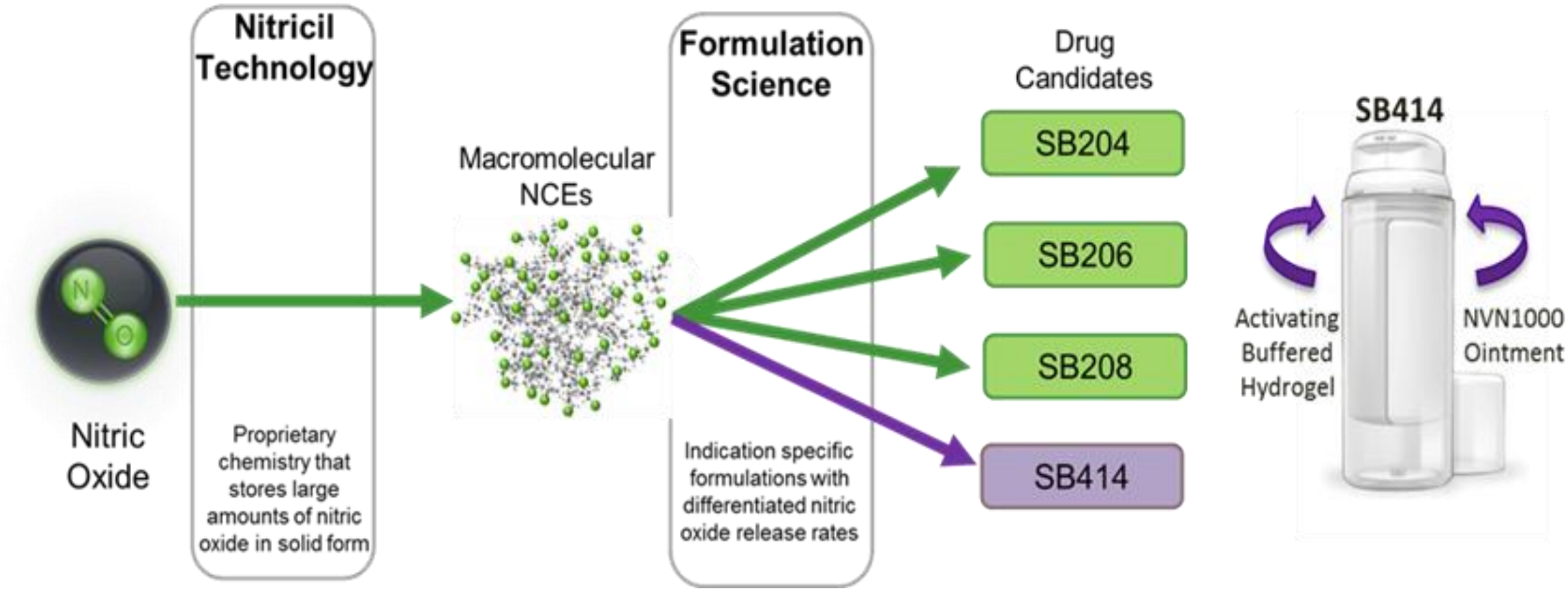
Broad Spectrum Antimicrobial

Modulator of Inflammation

Overcoming the Challenges with Nitric Oxide Delivery

Issues with Nitric Oxide Delivery	Our Nitricil Technology Addresses
Lack of tunability	✓
Unfavorable stability profile	✓
Low storage capacity	✓
Lack of targeting	✓
Backbone toxicity	✓

Nitricil Platform Technology



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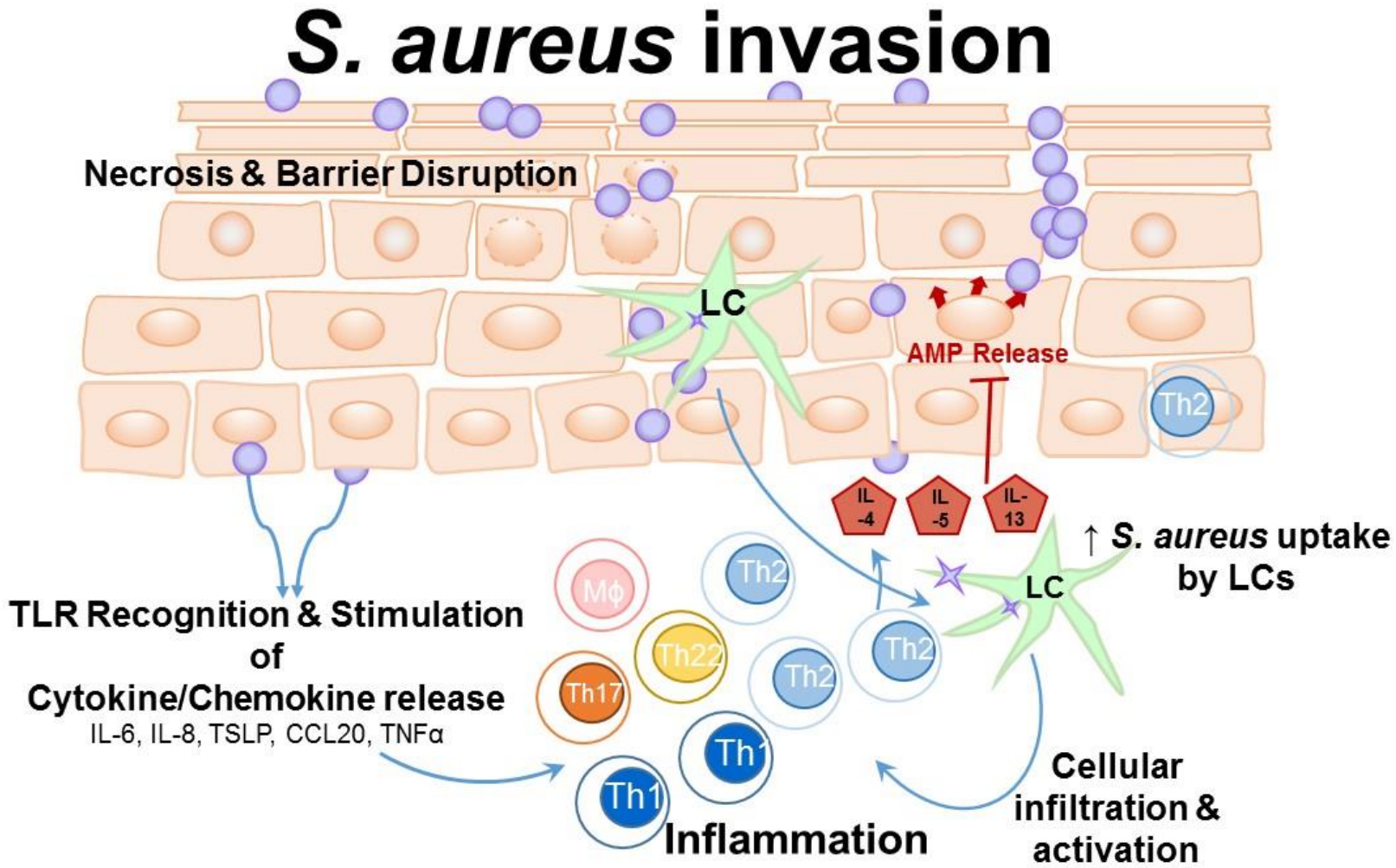
Atopic Dermatitis (AD):
Staphylococcus aureus & Disease Pathology



Adapted from Hepburn L, et al. Br J Dermatol. 2016 Oct 25 (epub ahead of print)

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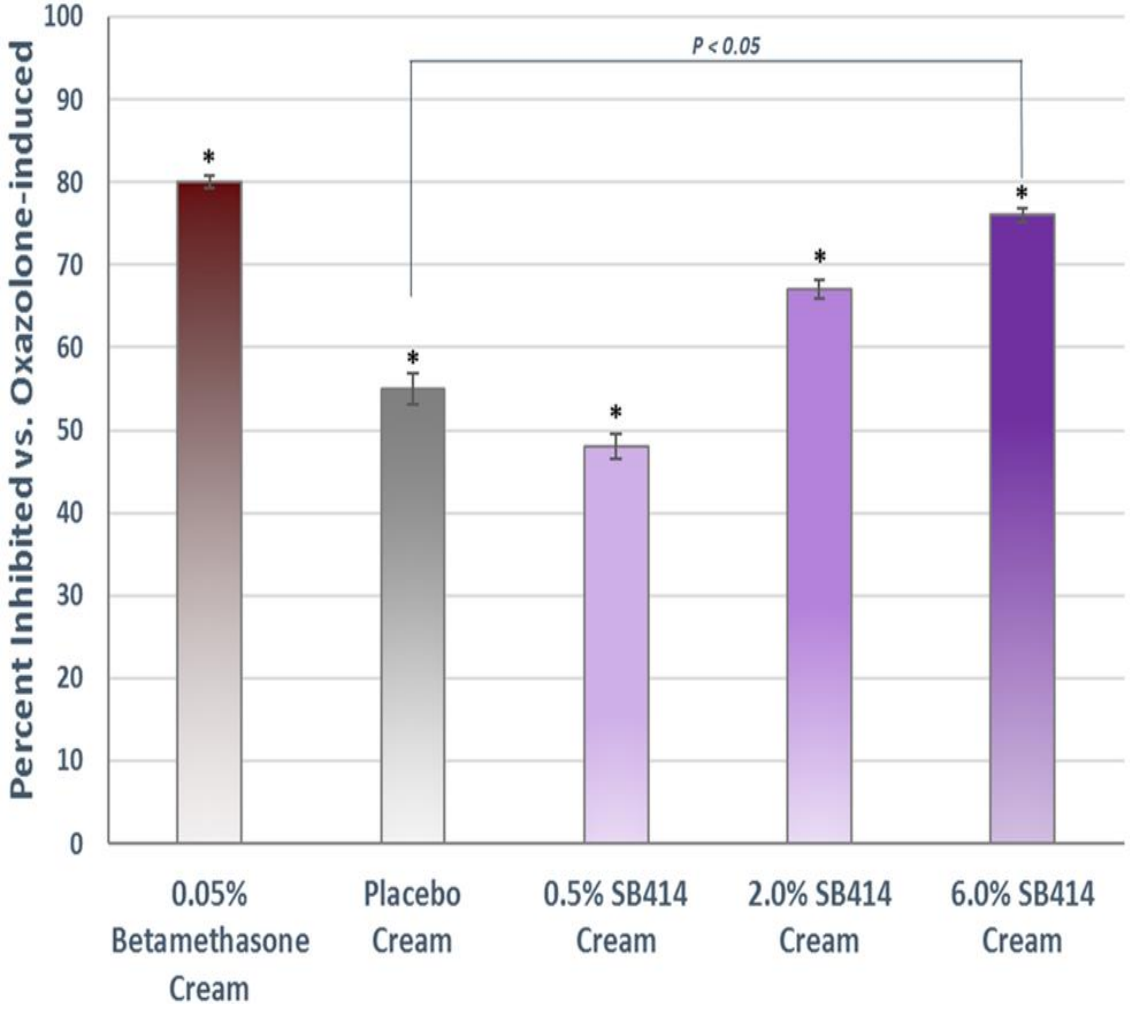
Topical Nitric Oxide Demonstrates Gross Anti-inflammatory Activity

- BALB/c Mice sensitized with Oxazolone (1.5% in acetone, Day 0)
- 7 days later – 2nd sensitization w/Oxazolone (1.0% in acetone)
- Topical treatments applied to right ear:
  - 30 minutes before 2nd sensitization
  - 15 minutes after 2nd sensitization
- 24 hrs. after 2nd oxazolone sensitization measure ear thickness (left & right) w/a dial thickness micrometer.
- Calculate percent inhibition vs. untreated animals



*p<0.05 vs. Untreated (Oxazolone-induced) animals

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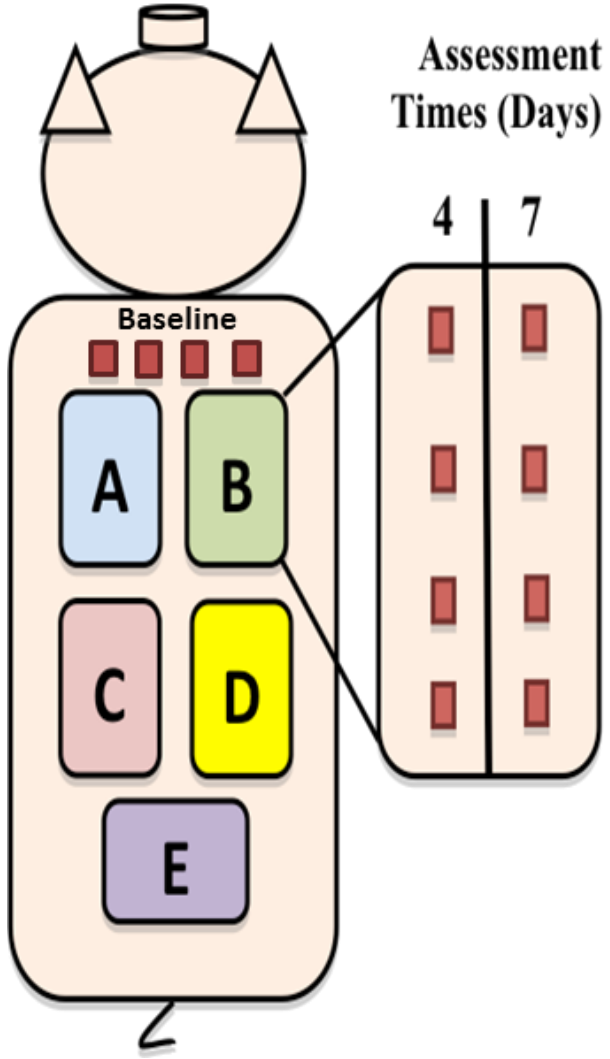
Biofilm-infected Partial Thickness Wound Model

- Partial thickness wounds generated via dermatome
- Inoculation of methicillin-resistant *S. aureus* isolated from lesion of AD patient
- Bacterial biofilms establish for 2 days prior to intervention
- Topical therapy applied once a day for 2 or 5 applications
- Bacteria recovered and quantified



A) 0.5% SB414 Cream

B) 2.0% SB414 Cream

C) 6.0% SB414 Cream

D) Placebo Cream

E) Untreated Control

Note- 48 hour biofilms was established prior to the first treatment application on Day 4. The dressings were changed daily after every morning treatment application.

Baseline wounds were recovered immediately before the 1st treatment application.

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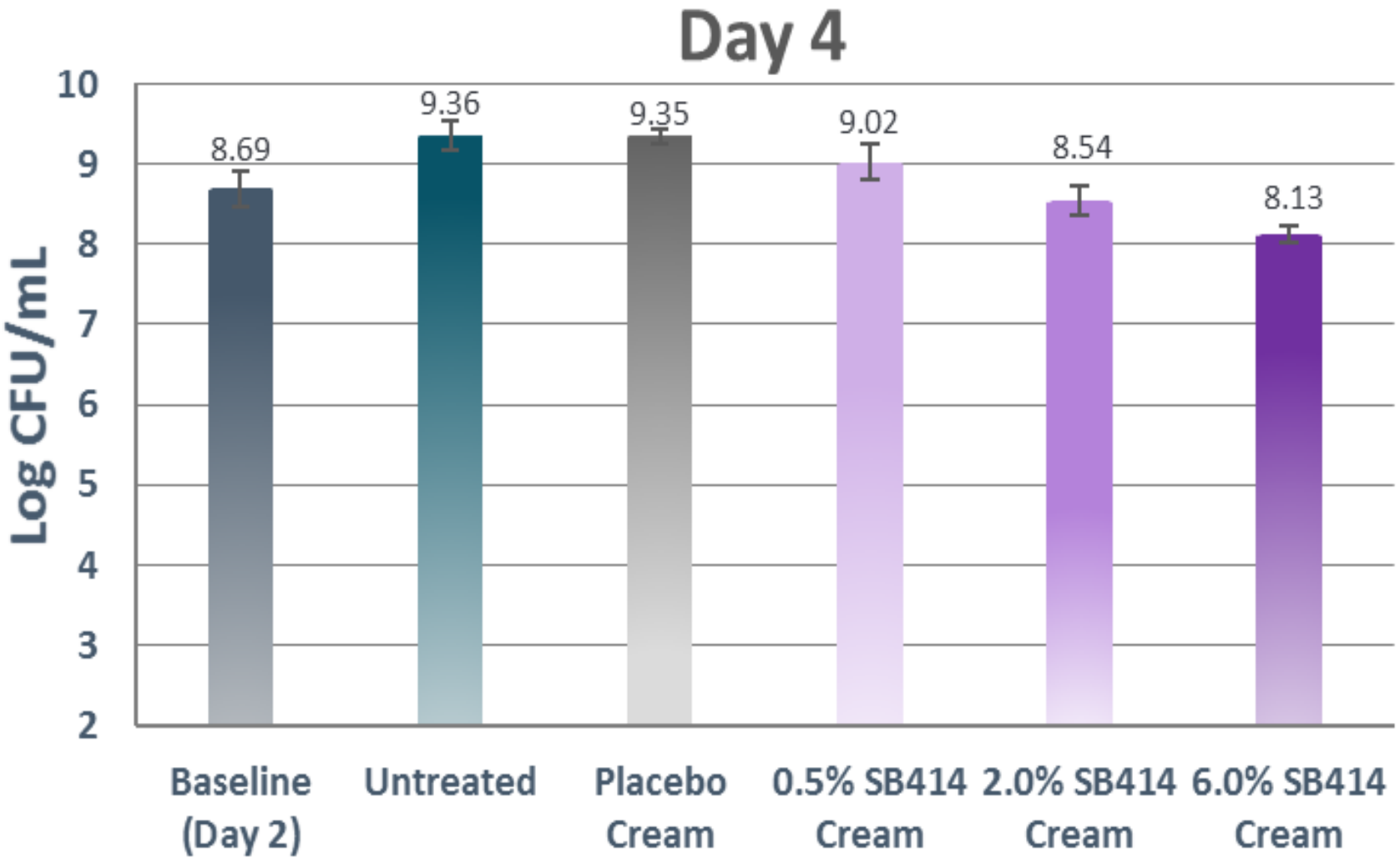
Reduction of AD-Specific *S. aureus* after Two Days of Treatment with SB414



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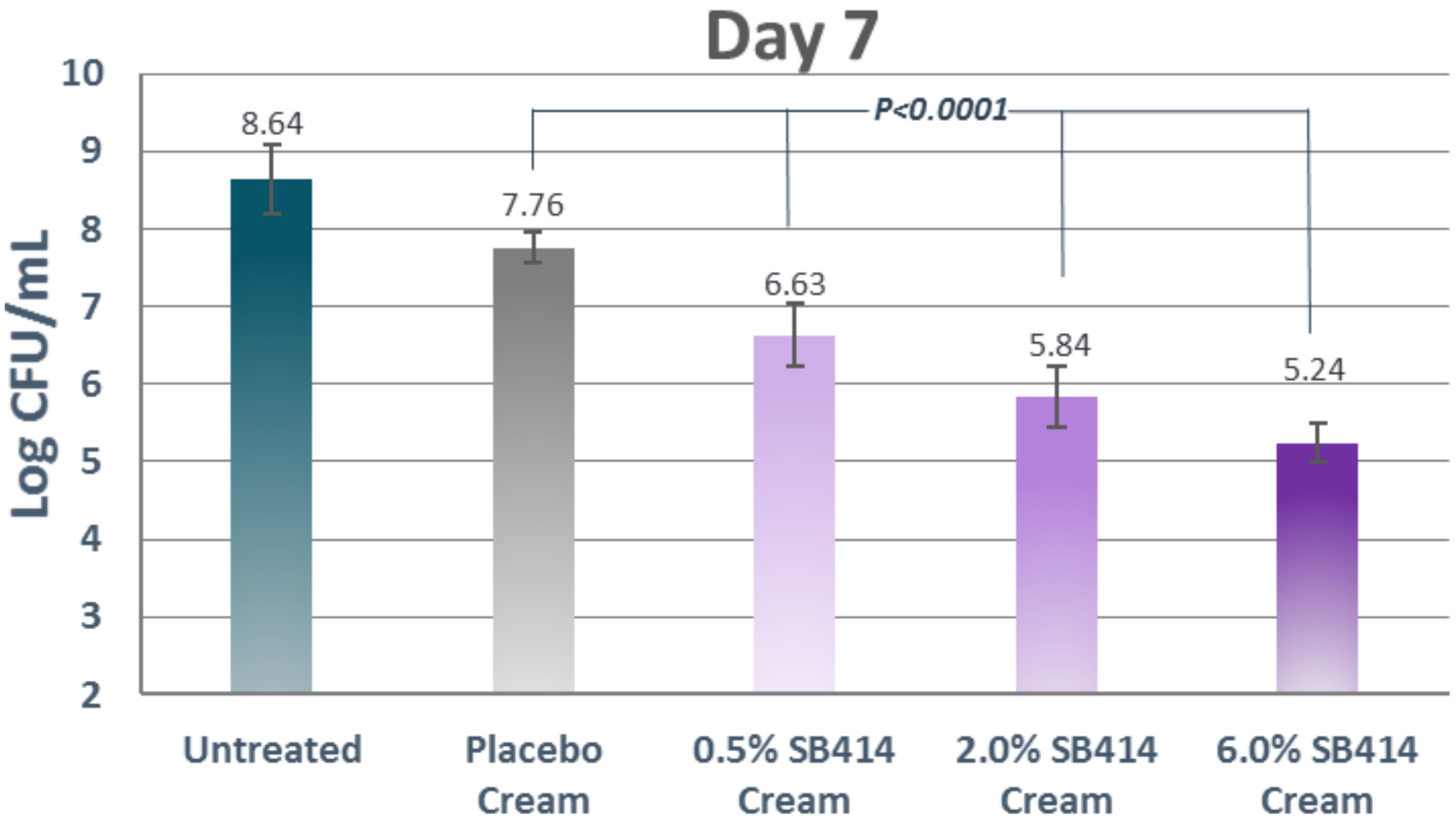
Reduction of AD-Specific *S. aureus* after Five Days of Treatment with SB414



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Conclusions

- *S. aureus* invades the epidermal and dermal layers of AD skin and contributes to disease severity by activating immune cells and stimulating production of inflammatory cytokines.
- A dose-dependent inhibition of gross inflammation was observed with SB414 Cream in the oxazolone-induced contact hypersensitivity model.
- At the same strengths, SB414 Cream demonstrates potent anti-staphylococcal activity reducing MRSA counts by greater than 99.9% at the highest dose following 5 topical applications.
- Topical nitric oxide therapy has the potential to target 2 important aspects of AD pathology.

MRSA - methicillin-resistant Staphylococcus aureus

Nitric Oxide for Topical AD Therapy

1. **Anti-microbial activity**

2. **Immunomodulatory Activity**
   - Inflammasome inactivation
   - NLRP3 activity in T_H2 cells?
   - Suppress DC and inflammatory cell infiltration

3. **Topical formulation with pH control**
   - Restore elevated AD skin pH[1] to acidic

4. **Self-emulsifying cream formulation**
   - Hydrating
   - Reduce Trans-epidermal water loss

5. **Promote terminal keratinocyte differentiation**[2]

1. Rippke, F. et al. Am. J. Clin. Dermatol. 2004;5(4):217-223.
2. Krischel, V. et al. J Invest. Dermatol. 1998;111(2):286-291.

Thank You