# Nitric Oxide-Releasing Topical Therapeutic for Atopic Dermatitis

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2017 Society for Investigative Dermatology (SID), Portland, Oregon. April 26-29, 2017.

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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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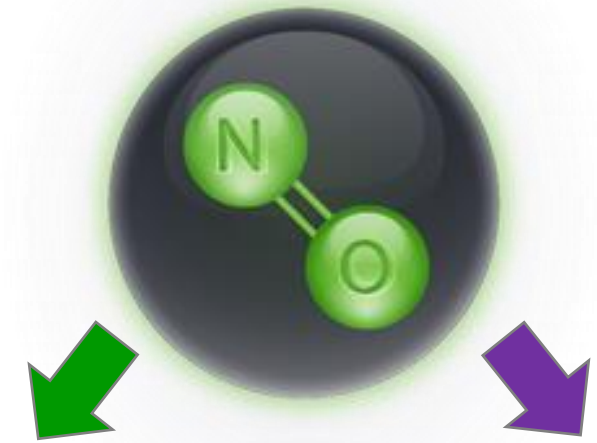
# Two Fundamental Mechanisms of Action of Nitric Oxide



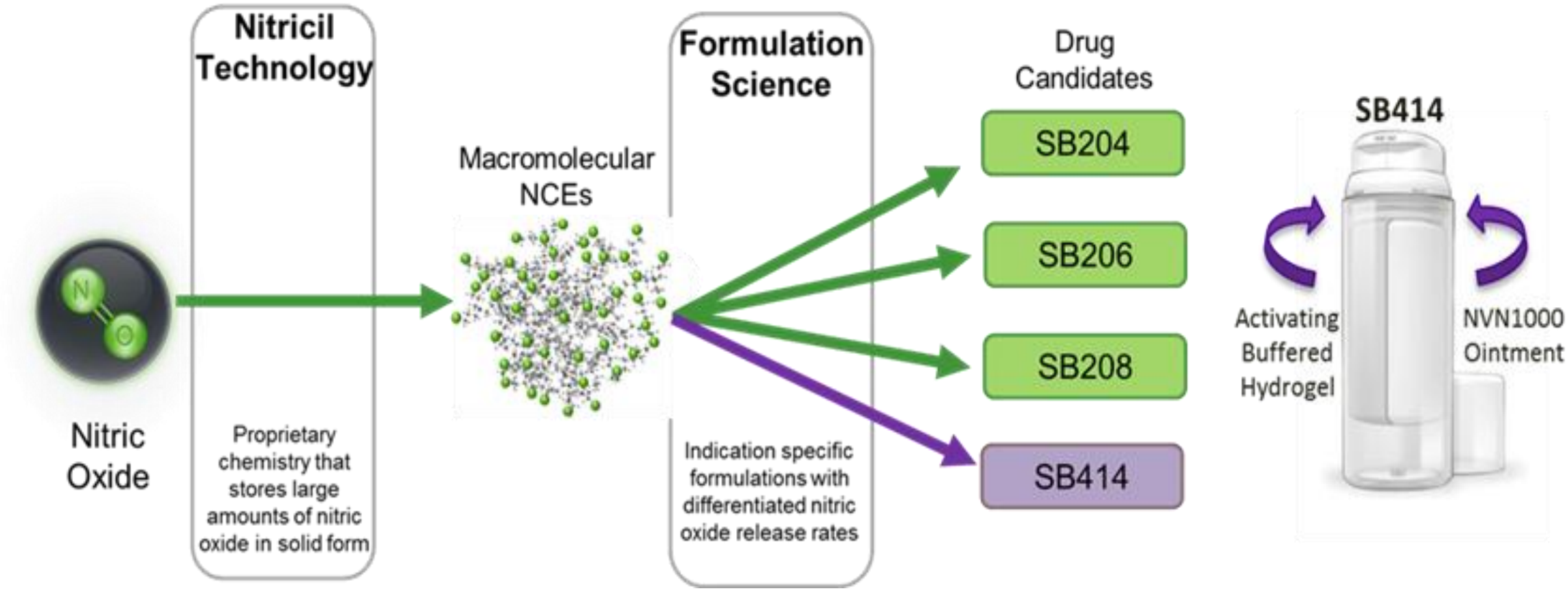

***Broad Spectrum Antimicrobial***

***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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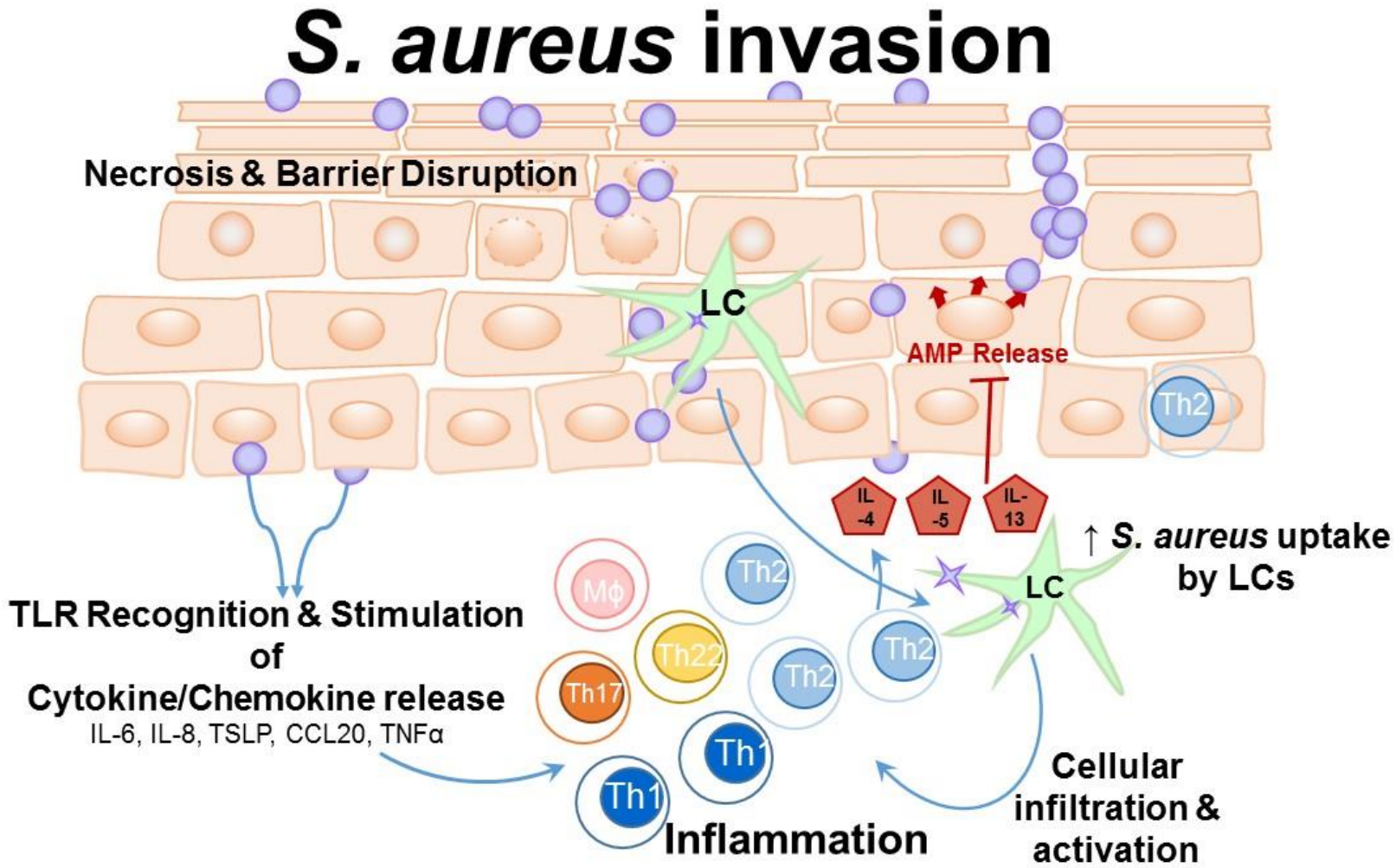
# Atopic Dermatitis (AD):
## *Staphylococcus aureus* & Disease Pathology




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

# Two Fundamental Mechanisms of Action of Nitric Oxide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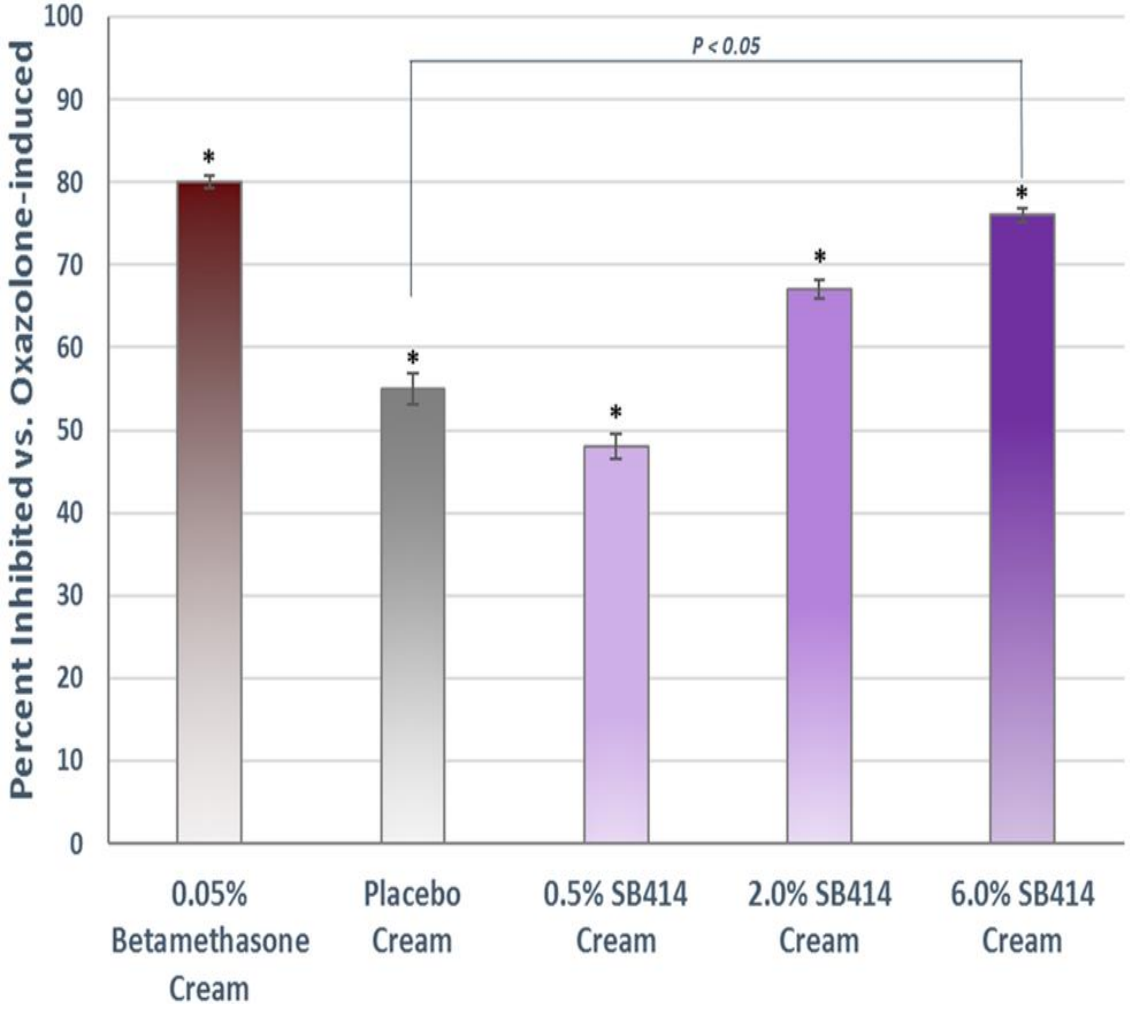
# Topical Nitric Oxide Demonstrates Gross Anti-inflammatory Activity

- 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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# Two Fundamental Mechanisms of Action of Nitric Oxide


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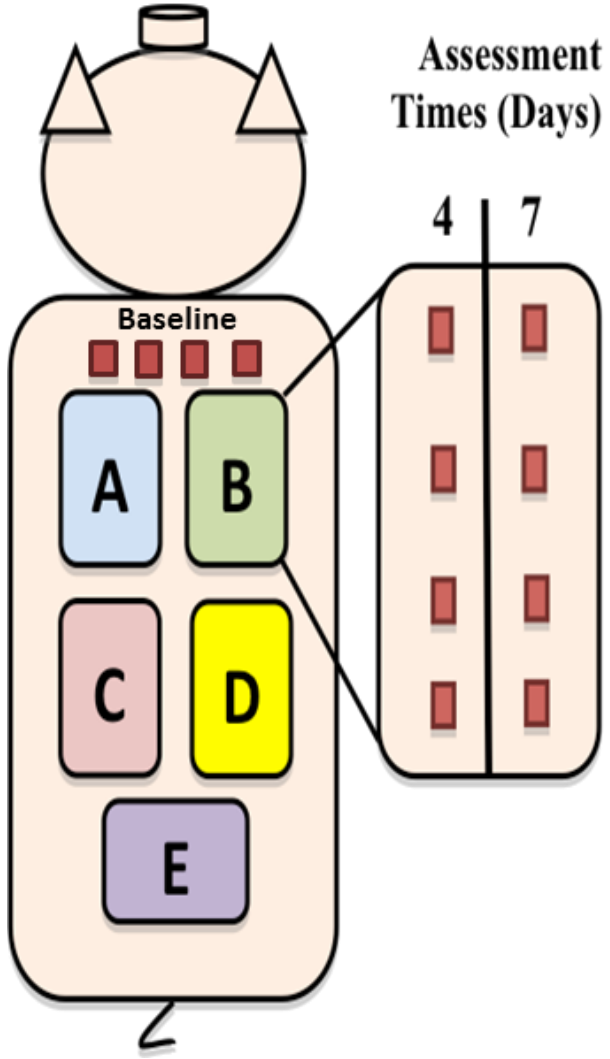
# Biofilm-infected Partial Thickness Wound Model

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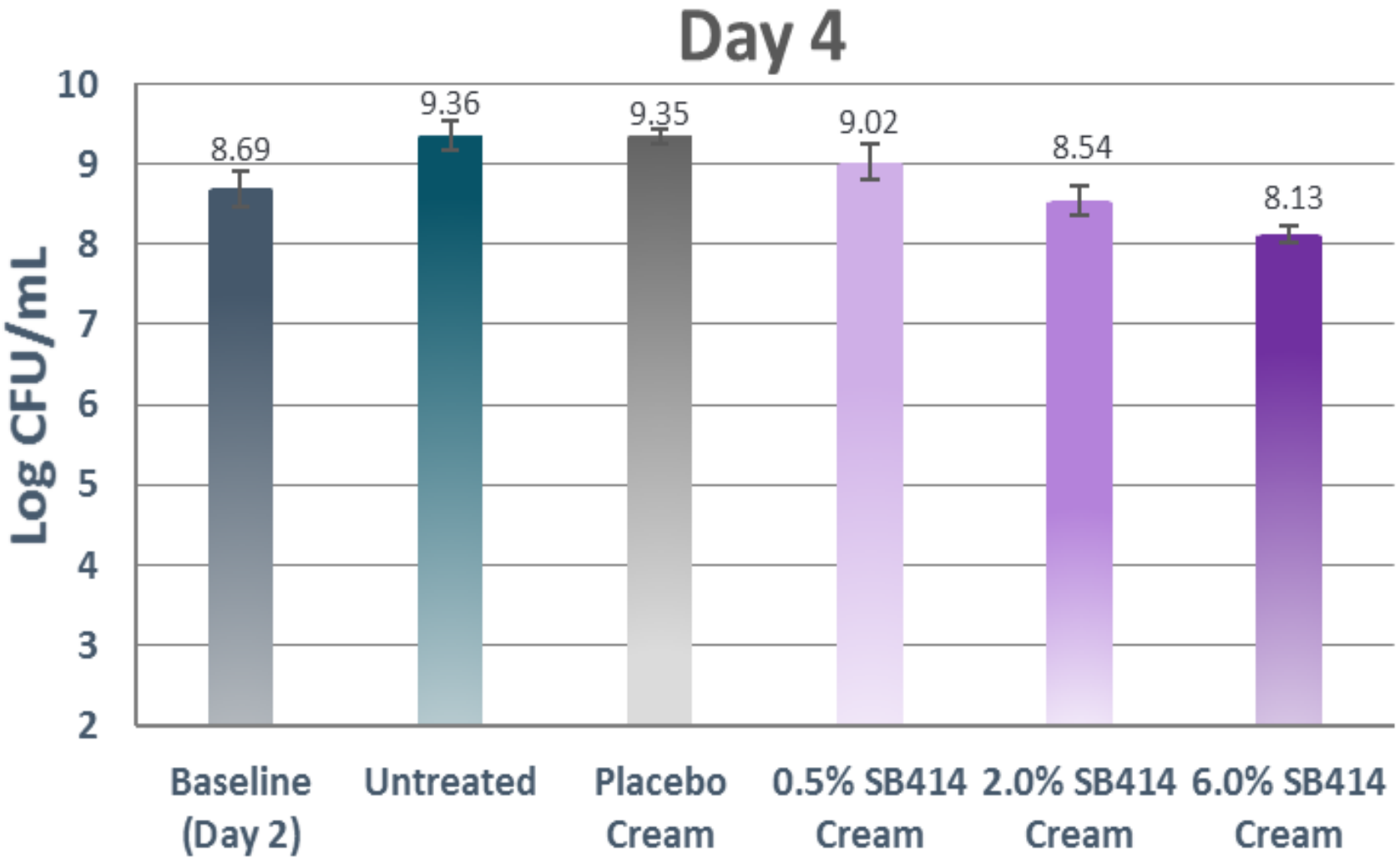
# Reduction of AD-Specific *S. aureus* after Two Days of Treatment with SB414

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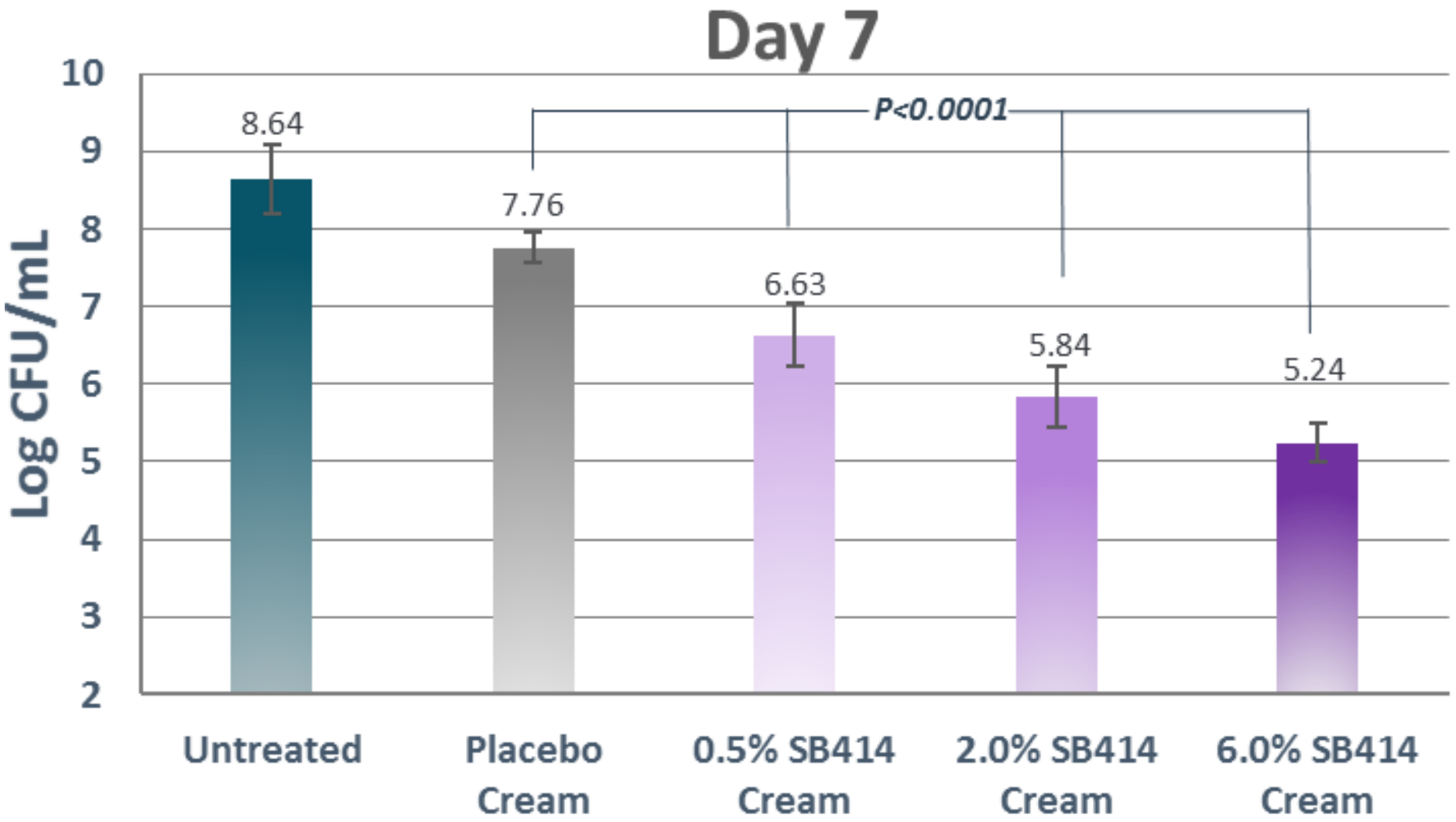
# Reduction of AD-Specific *S. aureus* after Five Days of Treatment with SB414

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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