

# Menopause and the Skin

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# Disclosures

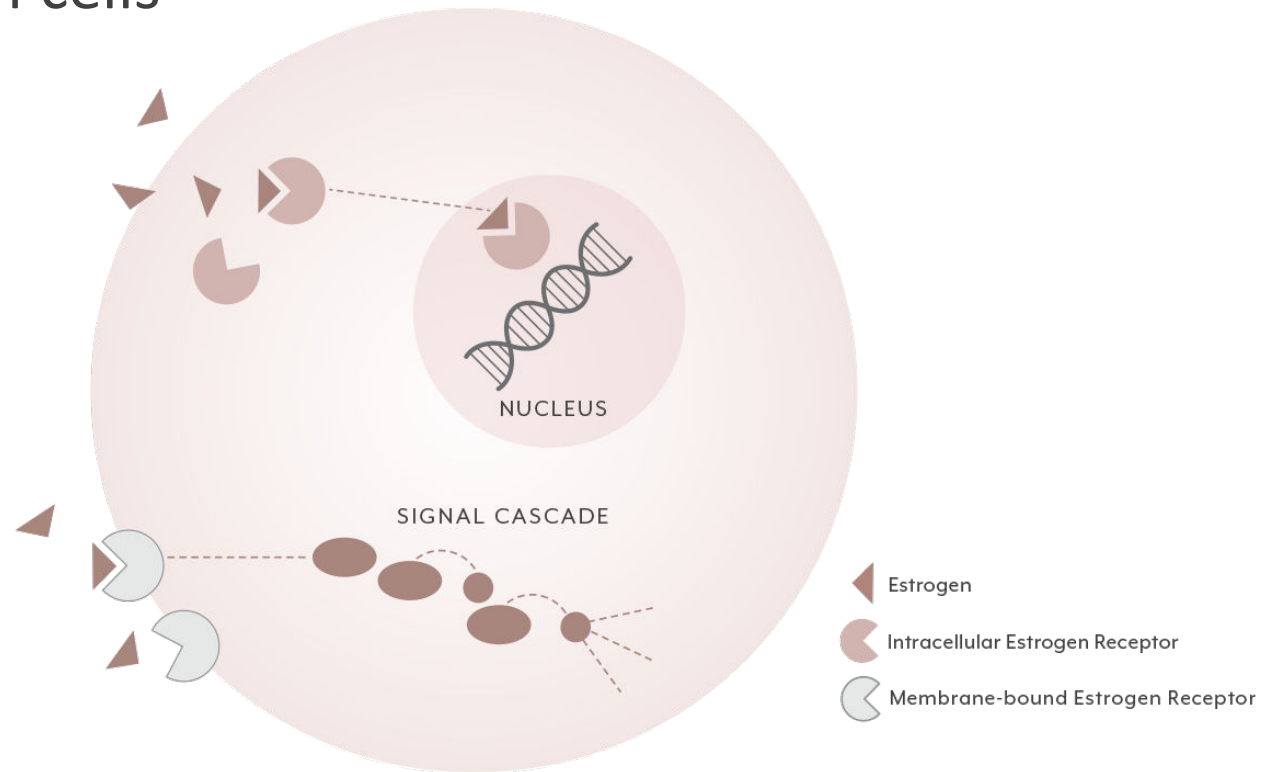
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- Allergan
- Galderma
- Ortho Derm
- Ferndale
- J & J
- L'Oreal
- Revance
- Top MD
- RegimenMD
- La Roche Posay
- SkinCeuticals
- Neutrogena

# Estrogen receptors and the skin<sup>1-2</sup>

## Estrogen receptors (ERs) in skin cells

- ER $\alpha$  and ER $\beta$   
(keratinocytes, fibroblasts, and cells of epidermal appendages)
- ER $\beta$  more widespread
- ER expression highest on face, scalp and vagina
- Estrogen increases ER expression



# ER signaling results in visible effects on skin

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Estrogen has been shown to<sup>1-4</sup>:

↑ skin rigidity, elasticity, wound healing

↑ hydration, epidermal thickness, blood flow

↑ extracellular matrix components

(collagen, elastin, fibrillin)

Evidence of estrogen's effect on skin comes primarily from studies of the application of exogenous estrogen to post-menopausal women

↑ moisture retention

(hyaluronic acid, mucopolysaccharides)

↑ thickness of cutaneous layers

(epidermis: keratinocyte proliferation, dermis: fibroblast proliferation)

↓ wrinkling

Estrogen is an essential component to skin functioning, health and wellness

**References:** 1. Hall G, Phillips TJ. *J Am Acad Dermatol*. 2005;53:555-68. 2. Wolff EF, Narayan D, Taylor HS. *Fertil Steril*. 2005;84:285-8. 3. Svoboda RM, Del Rosso JQ, Zeichner JA, Draelos ZD. *Skin*. 2018;2:308-16. 4. Draelos ZD. *Fertil Steril*. 2005;84(2):291-2.

# The picture of Estrogen Deficient Skin (EDS)<sup>1-3</sup>

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## Histological Changes

- Significant decrease in Collagen I & III and type 1 procollagen
- Decrease in glycoaminoglycan content
- Decrease in TGF- $\beta$ 1 expression
- Reduced expression of IGF-1 receptors and production of IGF-1
- Reduced ROS defense activity

## What the Patient Expects

- Dryness
- Pruritis
- Increased wrinkles
- Thinning
- Atrophy
- Impaired wound healing

**References:** 1. Hall G, Phillips TJ. *J Am Acad Dermatol*. 2005;53:555-68. 2. Thornton MJ *Dermo-Endocrinology*. 2013;5:2, 264-270 3. Rzepecki AK, Murase J, Juran R, Fabi S, McLellan B. "Estrogen Deficient Skin: The Role of Topical Therapy". *International Journal of Women's Dermatology*, 2019, in press.

# Estrogen-deficient Skin

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Estrogen deprivation in postmenopausal women accelerates:

- Dryness
- Atrophy
- Fine wrinkling
- Poor wound healing

Estrogen restores skin moisture via promotion of sebum secretion:

- By increasing insulin-like growth factor production, leading to lipogenesis in sebocytes and thus moisture retention)
- By increasing mucopolysaccharide and hyaluronic acid levels

# Significant collagen loss after onset of menopause<sup>1</sup>

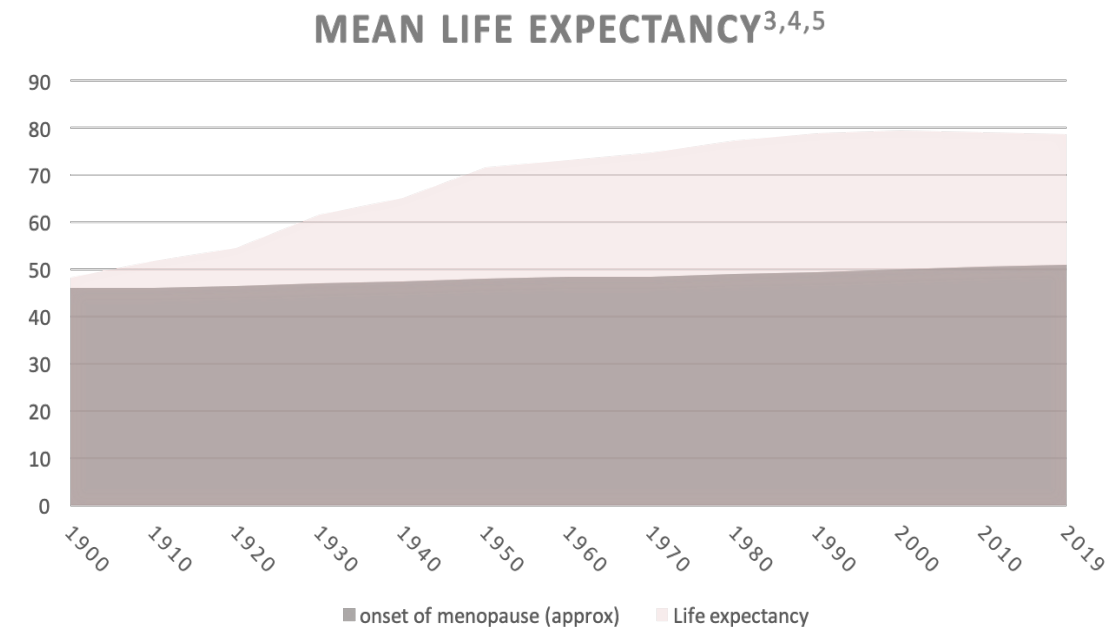


COLLAGEN LOSS IS MORE  
CLOSELY RELATED TO  
DURATION OF ESTROGEN  
DEFICIENCY THAN TO  
CHRONOLOGICAL AGE

**References:** 1. Archer DF. *Gynecol Endocrinol*. 2012;28(suppl 2):2-6. 2. Hall G, Phillips TJ. *J Am Acad Dermatol*. 2005;53:555-68. 3. Shu YY, Maibach HI. *Am J Clin Dermatol*. 2011;12:297-311.

# Importance is growing

- Mean life expectancy, now 76.8, has increased 30 years since 1900<sup>1</sup>
- Onset of menopause has been delayed by only 5 years in the same time so women spend more of life in menopause<sup>3</sup>
- In the US, approximately 1.3 million women become menopausal each year<sup>4</sup>
- In 2021, women aged 50 and over accounted for 26% of all women<sup>5</sup>



**References:** 1. Ten great public health achievements. United States, 2001-2010. *MMWR*. 2011;60:619-23. 2. 2011 Women's Health Stats & Facts. American Congress of Obstetricians and Gynecologists (ACOG). 3. From Menarche to Menopause: Trends among US Women Born from 1912 to 1969. Hazel B. Nichols Amy Trentham-Dietz John M. Hampton Linda Titus-Ernstoff Kathleen M. Egan Walter C. Willett Polly A. Newcomb, *American Journal of Epidemiology*, Volume 164, Issue 10, 15 November 2006, Pages 1003-1011, <https://doi.org/10.1093/aje/kwj282>, Published: 8/23/2006. 4. Life expectancy in the USA, 1900-98, [www.demog.berkeley.edu/~andrew/1918/figure2.html](http://www.demog.berkeley.edu/~andrew/1918/figure2.html). 5. Life expectancy in the USA, 1900-98. men and women. Year. M. F. 1900. 46.3. 48.3. 1901. 47.6. 50.6. 1902. 49.8. 53.4. 1903. 49.1. 52.0. 1904. 46.2. 49.1. 1905. 4. Peacock K, Ketvertis KM. Menopause. [Updated 2022 Aug 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK507826/> 5. <https://www.who.int/news-room/fact-sheets/detail/menopause>



# Addressing EDS with topical estrogen<sup>1-2</sup>

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## Topical estradiol & estradiolvalerate

- Indicated for VVA; use for EDS is off-label
- Concentrations of 0.01% - 0.062%
- Documented benefits for the skin including skin thickness, dryness, wrinkles, etc
- Risks of telangiectasias, irritation and tenderness
- Some evidence of systemic absorption and, therefore, the potential associated risks (coronary artery disease, stroke, cancer, etc)

**Reference:** 1. Svoboda RM, Del Rosso JQ, Zeichner JA, Draelos ZD. *Skin*. 2018;2:308-16. 2. AK Rzepecki, J Murase, R Juran, S Fabi, B McLellan, *International Journal of Women's Dermatology*, 2019, in press

# Effects of Topical Estradiol Cream

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The application of 0.01% estradiol cream to the face over a period of six months produced:

- A 23% increase in epidermal thickness<sup>1</sup>
- A 37% increase in epidermal thickness when applied with glycolic acid<sup>1</sup>

The application of 0.01% 17-beta estradiol to the face for 24 weeks produced:

- A significant increase in type I and type III collagen<sup>2</sup>
- A significant increase in hyaluronic acid concentration<sup>3</sup>

**References:** 1. Fuchs K.O., Solis O., Tapawan R., Paranjpe J. The effects of an estrogen and glycolic acid cream on the facial skin of postmenopausal women: A randomized histologic study. *Cutis*. 2003;71(6):481–488. 2. Silva L.A., Carbonel A.A., de Moraes A.R.B., Simões R.S., Sasso G.R.D.S., Goes L. Collagen concentration on the facial skin of postmenopausal women after topical treatment with estradiol and genistein: A randomized double-blind controlled trial. *Gynecol Endocrinol*. 2017;33(11):845–848. 3. Patriarca M.T., Barbosa de Moraes A.R., Nader H.B., Petri V., Martins J.R., Gomes R.C. Hyaluronic acid concentration in postmenopausal facial skin after topical estradiol and genistein treatment: A double-blind, randomized clinical trial of efficacy. *Menopause*. 2013;20(3):336–341.

# Hormone Replacement Therapy via Patch

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- A 12 month trial showed that post-menopausal women receiving continuous treatment of 17-beta estradiol via a patch on their forearm, along with cyclic medroxyprogesterone acetate, experienced a significant increase in their skin elasticity compared to baseline

**Reference:** Sumino H, Ichikawa S, Kasama S, Takahashi T, Kumakura H, Takayama Y, Kanda T, Murakami M, Kurabayashi M. Effects of raloxifene and hormone replacement therapy on forearm skin elasticity in postmenopausal women. *Maturitas*. 2009 Jan 20;62(1):53-7. doi: 10.1016/j.maturitas.2008.10.005. Epub 2008 Nov 29. PMID: 19042101.

# Addressing EDS with SERMs<sup>1</sup>

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## Selective estrogen receptor modulators (SERMs) <sup>1</sup>

- Phytoestrogens (soy, isoflavones, genistein)
- Lack evidence of ER activation
- Most positive effects were increased hydration & improvement in wrinkles
- Most data regarding increased collagen and improved epidermal thickness as not significant
- Effects most likely due to vehicle or antioxidant activity

In a 12-week study of 234 postmenopausal women applying isoflavone cream, skin dryness and roughness was improved<sup>2</sup>

**Reference:** 1. Svoboda RM, Del Rosso JQ, Zeichner JA, Draelos ZD. *Skin*. 2018;2:308-16. 2. AK Rzepecki, J Murase, R Juran, S Fabi, B McLellan, *International Journal of Women's Dermatology*, 2019, in press 2. Rzepecki AK, Murase JE, Juran R, Fabi SG, McLellan BN. Estrogen-deficient skin: The role of topical therapy. *Int J Womens Dermatol*. 2019 Mar 15;5(2):85-90. doi: 10.1016/j.ijwd.2019.01.001. PMID: 30997378; PMCID: PMC6451761.

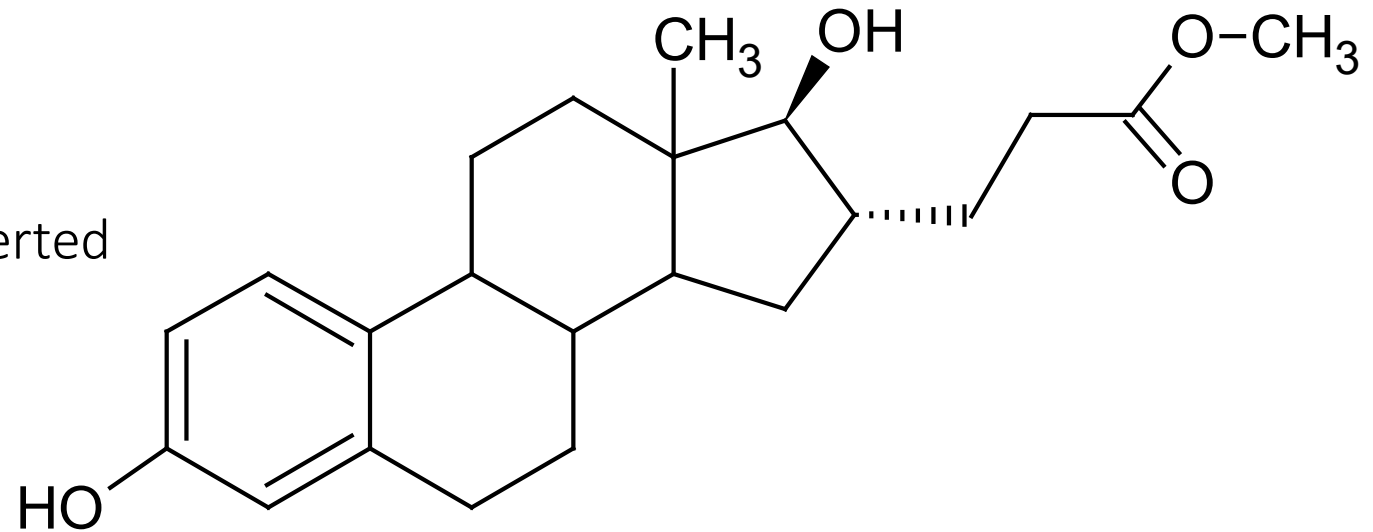
# MEP Technology

## Synthetic estrogenic sterol ester

- 1% ER $\beta$  binding affinity of estradiol
- No “off target” activity: rapidly converted by hydrolytic enzymes to inactivated hydrolysis carboxylic enzymes

## A new class of cosmeceutical agent

Non-hormonal Estrogen  
Receptor Agonist (NERA)



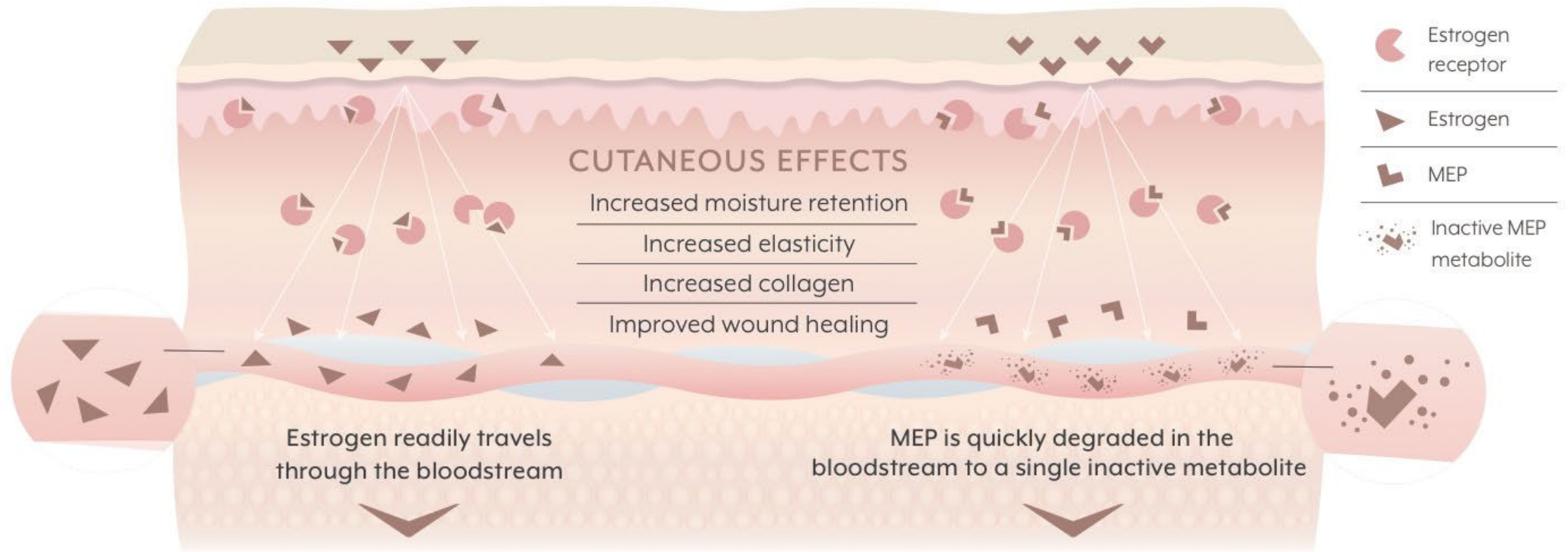
## Methyl Estradiolpropanoate (MEP):

Methyl 3-((8R,9S,13S,14S,16R,17S)3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-16-yl)propanoate

# ESTROGEN

VS.

# MEP



## ESTROGEN → SYSTEMIC EFFECTS

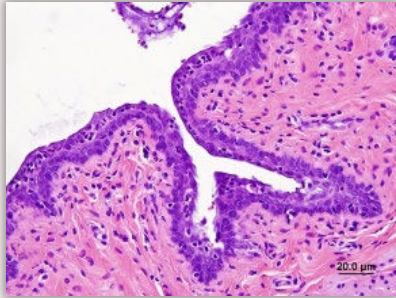
Cutaneous and systemic effects

- Reactivation of the menstrual cycle
- Increased risk of heart disease
- Proliferation of uterine endometrium
- Increased risk of cancer

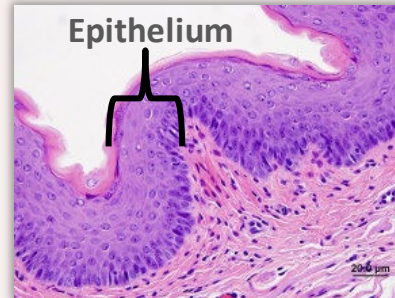
## MEP → NO SYSTEMIC EFFECTS

Cutaneous effects only

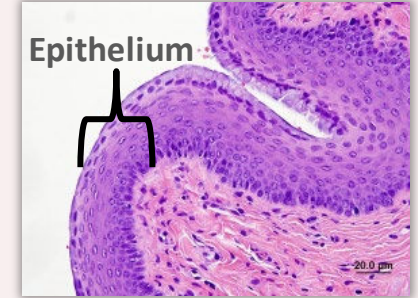
# Promising preclinical data for MEP precursor



Vehicle Control | Rat 27316



Estradiol 10 µg/kg | Rat 27337



“Compound C” 100 µg/kg | Rat 27314

“Compound C” is a molecule of similar structure to MEP and used for clinical proof of concept studies

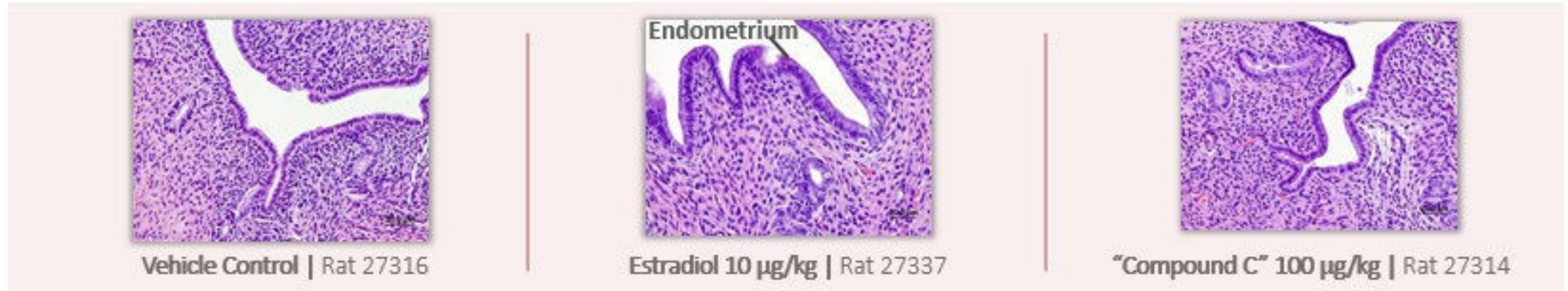
## Preclinical findings:

- Produced the same healthy thickening response of the epithelium and vaginal wall subtypes as estradiol

NOTE: MEP has not been and will not be tested on animals.



# Promising preclinical data for MEP precursor, cont.



“Compound C” is a molecule of similar structure to MEP and used for clinical proof of concept studies

Preclinical findings:

- No undesired effect on the uterus at supra-therapeutic doses
- Subcutaneous dosing indicated potential for large safety margin compared to estradiol

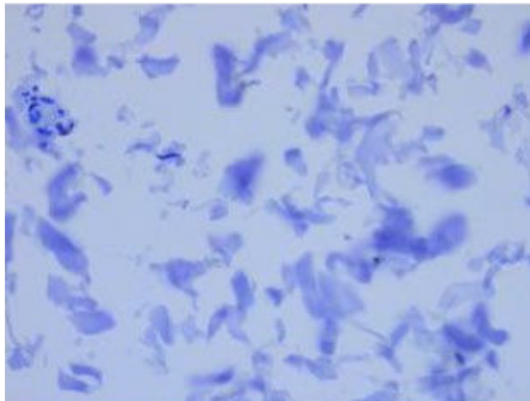
NOTE: MEP has not been and will not be tested on animals.



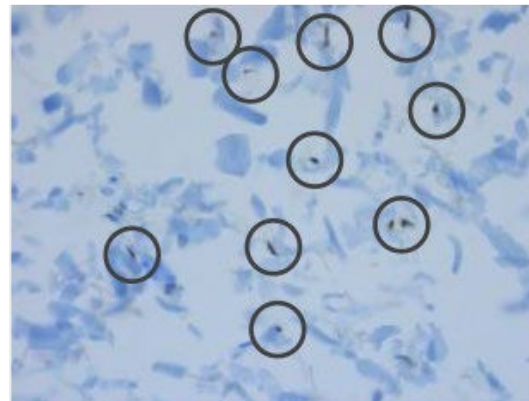
# Upregulation of Fibroblast ER expression

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Fibroblast ER positivity: estrogen receptor expression before and after MEP Treatment



BASELINE: no ER (+) fibroblasts



14 WEEKS' MEP: 11 ER (+) fibroblasts

Slides courtesy of:  
Garron J. Solomon, MD  
CEO, Laboratory Director,  
Director of Dermatopathology  
Tripoint Diagnostics, PLLC,  
Morristown, NJ

# Product Categories

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- Sunscreen
- Hydration/barrier repair
- Antioxidant
- Anti-inflammatory
- Collagen repair
- Diet, hydration, exercise, sleep, stress reduction, dental hygiene, environmental factors