Docket #: S19-265

A Novel Peptide to Boost Epithelial Barrier Protection and Prevent Infections

Stanford researchers have developed EphrinA3 technology to strengthen epithelial barriers by increasing expression of cell-cell adhesion molecules, particularly desmoglein-1 (DSG1) and desmocollin-1 (DSC1). The vagina is lined by stratified squamous epithelium (SSE) that protects against mechanical injury and microbial infection (e.g. HIV, HSV, etc.). Circulating estrogen supports these functions, but the loss of estrogen caused using progestin-only contraceptives or onset of menopause promotes both loss of desmosome expression and the epithelial barrier, which increases susceptibility to sexually transmitted infections.

Stanford investigators discovered ephrin A3 (EFNA3) mimetic agonist peptides (EFNA3-MAP) that promote desmosome expression and strengthen the epithelial barrier. Intravaginal administration of these agents to progestin-treated or ovariectomized mice reversed the loss of vaginal epithelial barrier protection in these mice caused by lower levels of circulating estrogen. Researchers also found cutaneous EFNA3-MAP topical application reduced allergen-specific IgE in a mouse atopic dermatitis model, suggesting potential clinical utility for enhancing epithelial barrier protection.

This nonsteroidal, nonhormonal EFNA3-MAP technology has the potential to treat a range of skin conditions caused by epithelial barrier dysfunction, and improve vaginal epithelial health in women using progestin-only contraceptives (e.g., Depo-Provera), menopausal or postmenopausal women, and women with ovarian failure due to chemotherapy.

Stage of Development: Research in vivo

Researchers demonstrated treatment with EFNA3-MAP increased DSG1/DSC1 expression, and improved epithelial barrier function. In mouse models, they showed

EphrinA3 treatment protected mice from HSV infection, improved vaginal epithelial integrity in a mouse model of menopause, and improved skin barrier function in a model of atopic dermatitis. Research is ongoing including toxicity studies and methods for sustained release.

Applications

- Non-Hormonal, non-steroidal therapeutic treatment and prevention of:
  - Sexually transmitted infections
  - Vaginal atrophy
  - Skin diseases and conditions, such as atopic dermatitis
  - Allergic diseases
- Barrier function enhancement of epithelial surfaces, including skin and genital mucosa
- Management of epithelial barrier dysfunction

Advantages

- Low-cost, non-hormonal, non-steroidal approach to addressing multiple medical conditions associated with compromised epithelial barriers.
  - Reduces susceptibility to genital pathogens, including HSV and HIV, through the promotion of genital mucosal barrier function
  - Decreases sensitization in atopic dermatitis
  - Non-estrogen treatment for the genitourinary syndrome of menopause
- Topical administration easily adaptable to topical delivery or release from intravaginal rings

Publications

- *New 2025 Publications!*
  - Liu, M., Miguel, R. D. V., Aceves, K., & Cherpes, T. L. (2025). Exogenous ephrin-A3 reverses loss of vaginal epithelial barrier protection in progestin-treated mice. *Mucosal Immunology*.
  - Liu, M., Charek, J. G., Vicetti Miguel, R. D., & Cherpes, T. L. (2025). Ephrin-Eph signaling: an important regulator of epithelial integrity and barrier

function. *Tissue Barriers*, 2462855.
- Quispe Calla, N. E., Vicetti Miguel, R. D., Aceves, K. M., Huang, H., Howitt, B., & Cherpes, T. L. (2021). Ovariectomized mice and postmenopausal women exhibit analogous loss of genital epithelial integrity. *Tissue Barriers*, 9(2), 1865760.
- Quispe Calla, N. E., Vicetti Miguel, R. D., Boyaka, P. N., Hall-Stoodley, L., Kaur, B., Trout, W., Pavelko S. D., & Cherpes, T. L. (2016). Medroxyprogesterone acetate and levonorgestrel increase genital mucosal permeability and enhance susceptibility to genital herpes simplex virus type 2 infection. *Mucosal immunology*, 9(6), 1571-1583.

Patents

- Published Application: WO2021071979
- Published Application: 20220362330

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