Development of a gel-forming vaginal estradiol formulation for the treatment of post-menopausal vaginal atrophy

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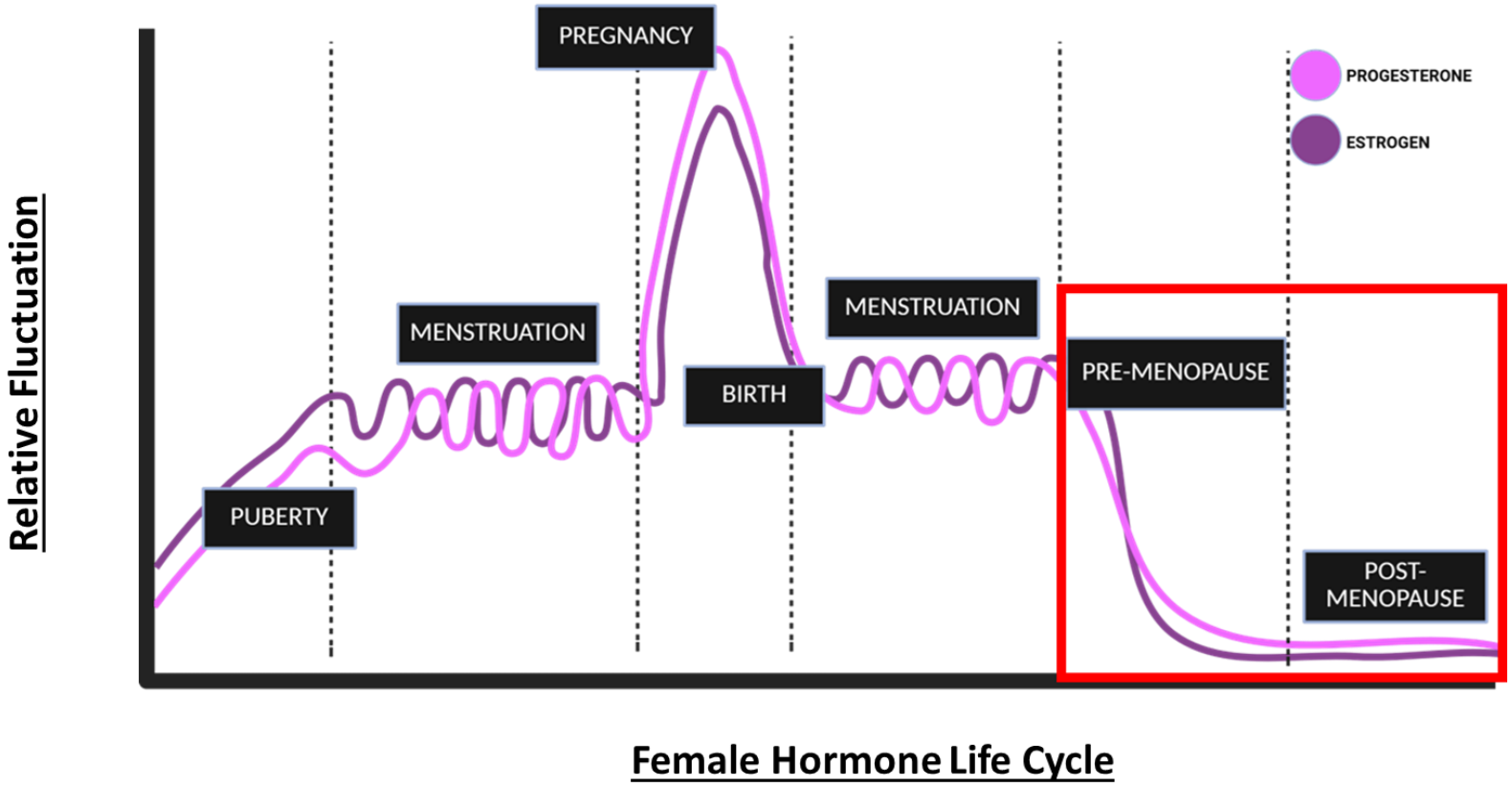
NEXT-GENERATION DELIVERY INNOVATIONS

Vaginal atrophy affects 27-84% of women post-menopause



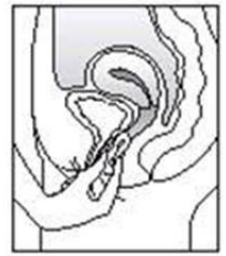
Female Hormone Life Cycle

- Dryness
- Painful intercourse
- Dysbiosis/Infection
- Recurrent UTI

Hormone therapy: Current options are limited and increase local inflammation

Creams (Estrace), suppositories, and moisturizers

Vaginal rings



Efficacy of Vaginal Estradiol or Vaginal Moisturizer vs Placebo for Treating Postmenopausal Vulvovaginal Symptoms

A Randomized Clinical Trial

Caroline M Mitchell [1,2,✉], Susan D Reed [3], Susan Diem [4,5], Joseph C Larson [6], Katherine M Newton [7], Kristine E Ensrud [4,8], Andrea Z LaCroix [9], Bette Caan [10], Katherine A Guthrie [6]

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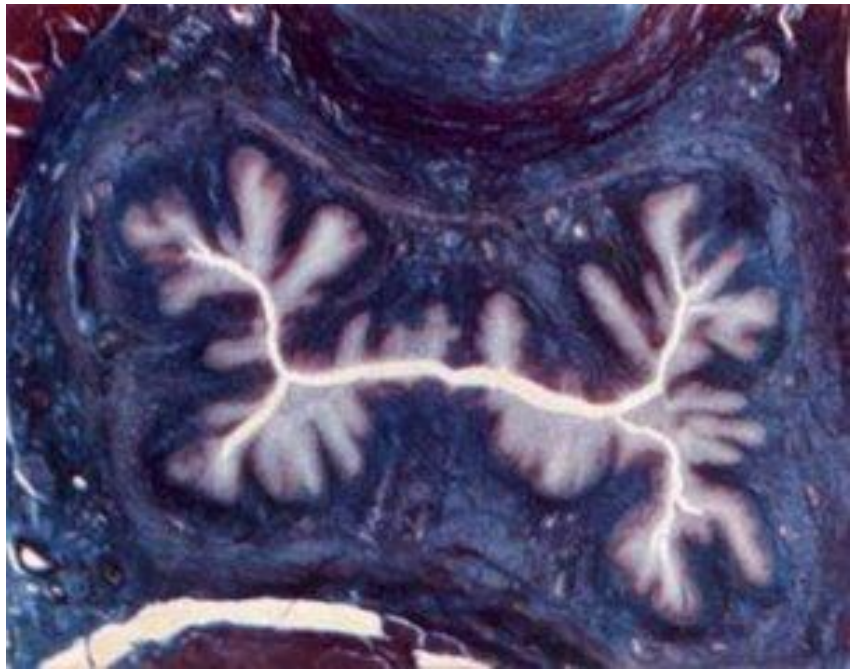
Conclusions and Relevance

Our results suggest that neither prescribed vaginal estradiol tablet nor over-the-counter vaginal moisturizer provides additional benefit over placebo vaginal tablet and gel in reducing postmenopausal vulvovaginal symptoms.

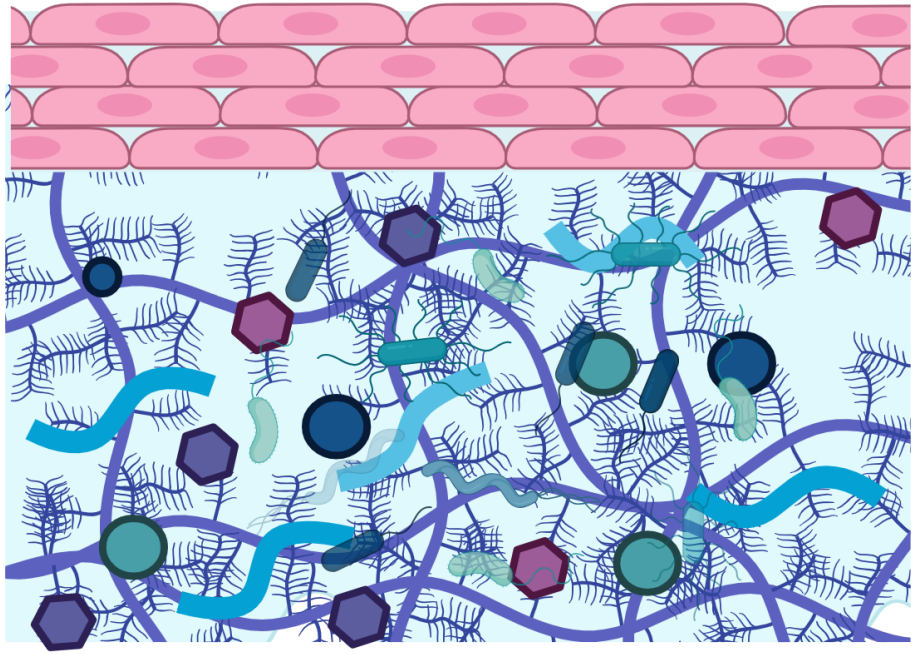
- Epithelial in
- Poor retenti
- Excess viscous white discharge

urogenital and
r symptoms
- Expulsion risk, limits options for patients with sag/prolapse.

Barriers to vaginal drug delivery: sticky pockets

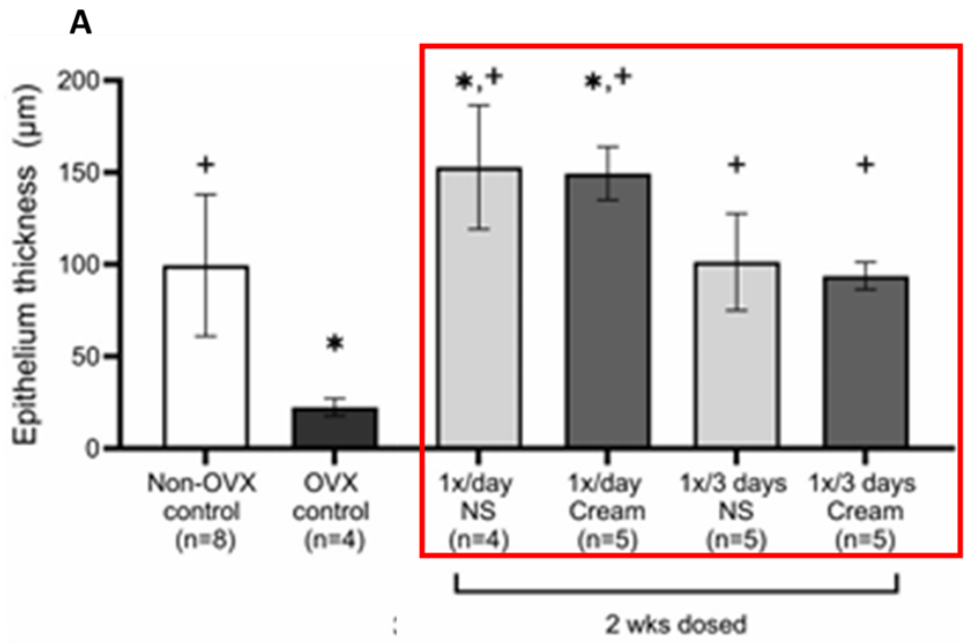


Vaginal Cross Section: Increased surface area due to high folding (folding) and pressurized collapse of epithelium.

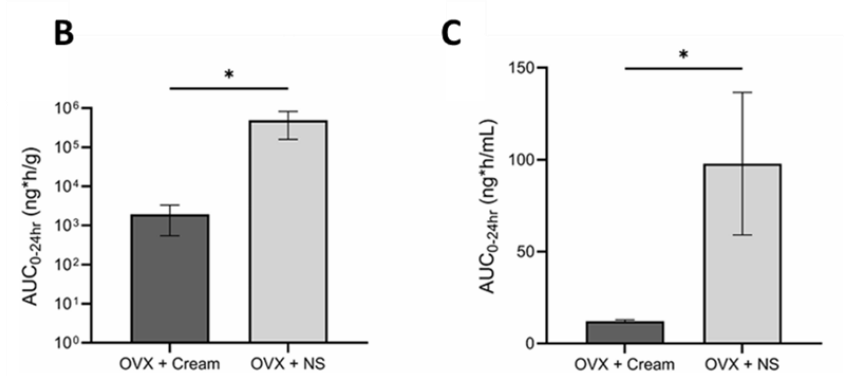


Endocervical Mucus Mesh: Steric and ionic mucin interactions trap particles and pathogens- can't reach cells.

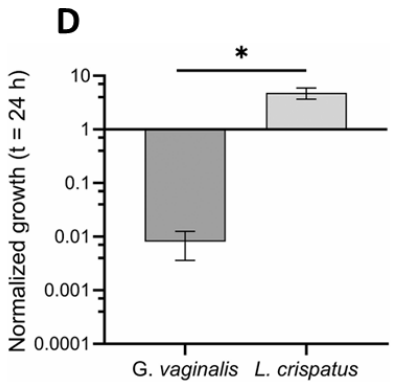
An F127 E2 nano-formulation was non-inferior to conventional therapy, with added benefit



Re-epithelialization of vaginal tissue.



Estradiol levels in tissue (B) and plasma (C).



Growth of L. crispatus **(typical) v.s. *G. vaginalis*** **(opportunistic) following drug exposure.**

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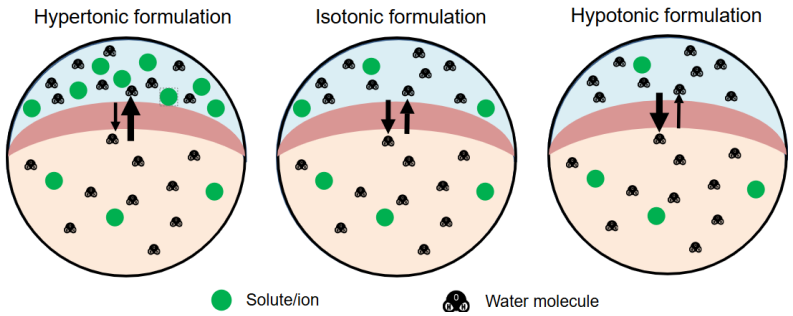
Formulating a more typical vaginal product with *in situ* gelling

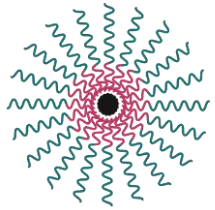
I. Spread and coverage of a liquid formulation upon application, with the retention of gel product.

II. Clear and retained polymer solution that eliminates unpleasant, white viscous discharge experienced with cream formulations.

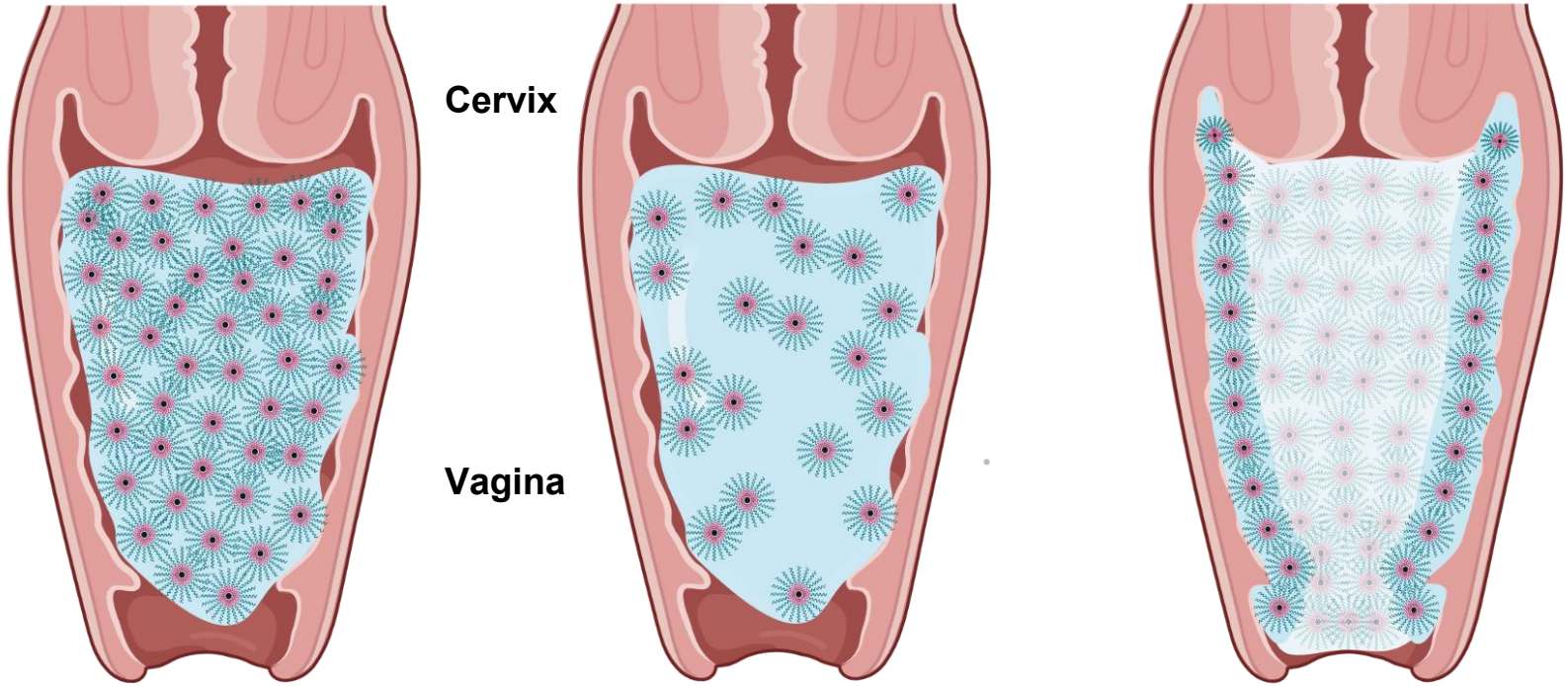
III. Potential for reaching therapeutic tissue levels at lower concentrations of estradiol.

Hypotonic F127 forms a concentrated gel *in vivo* due to epithelial water absorption aided by thermo-sensitivity

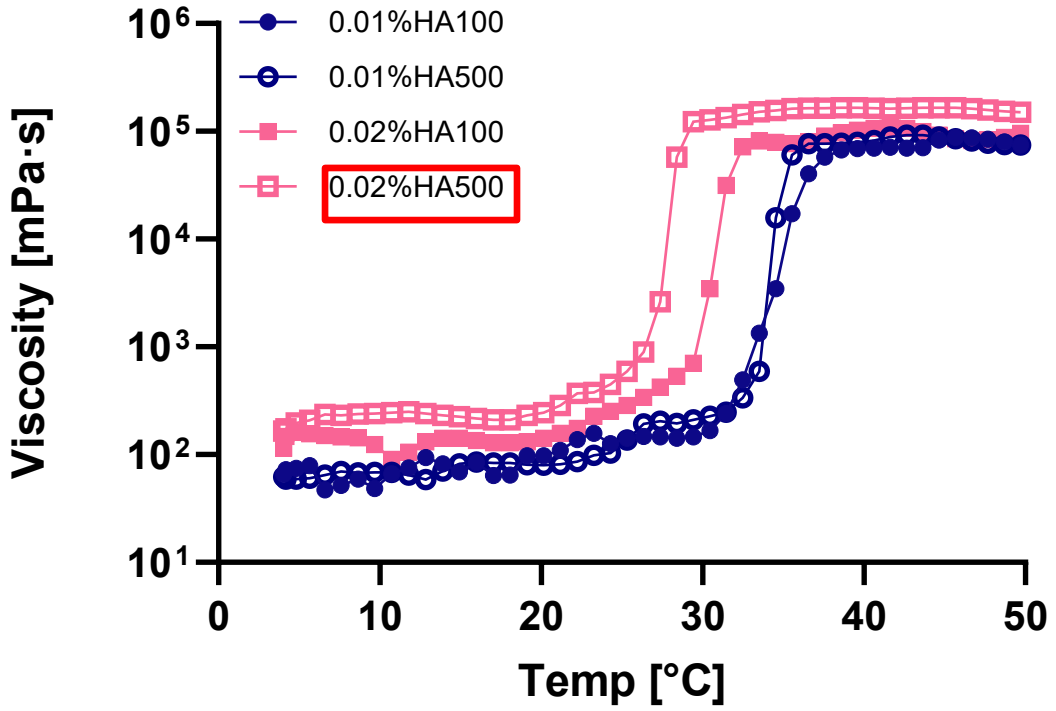


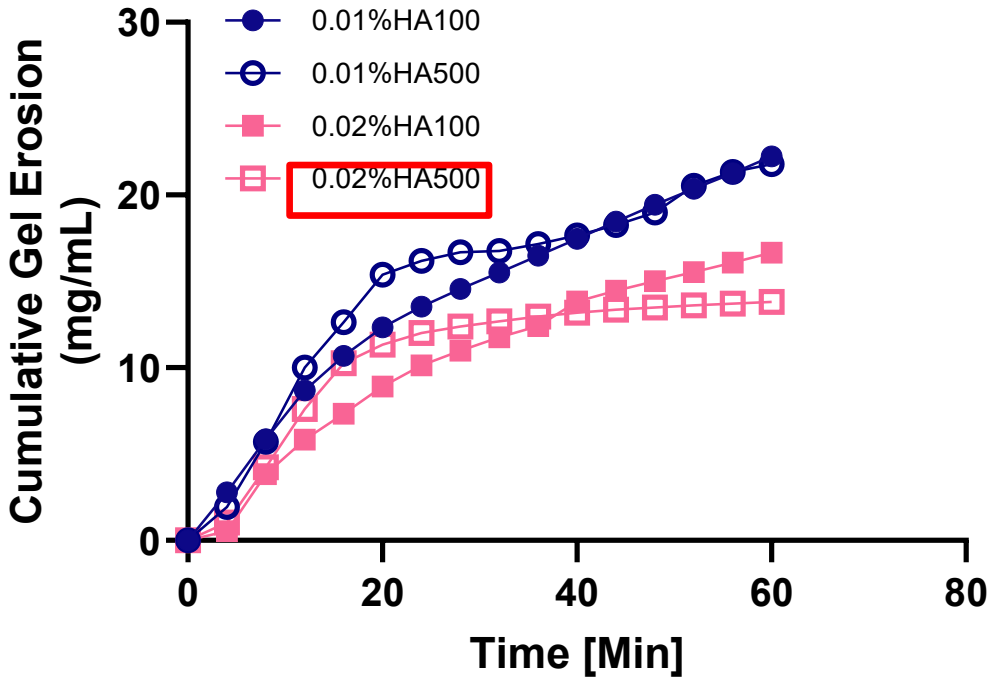


F127 Micelle



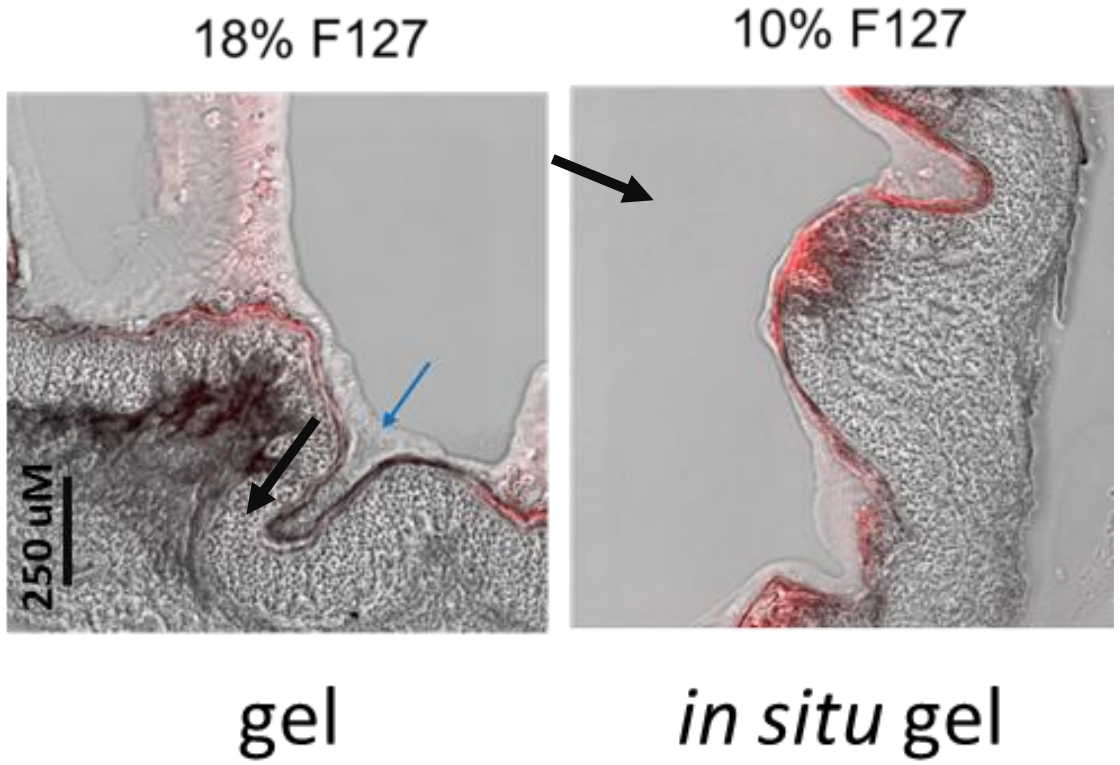
High MW hyaluronic acid improves viscosity and erosion

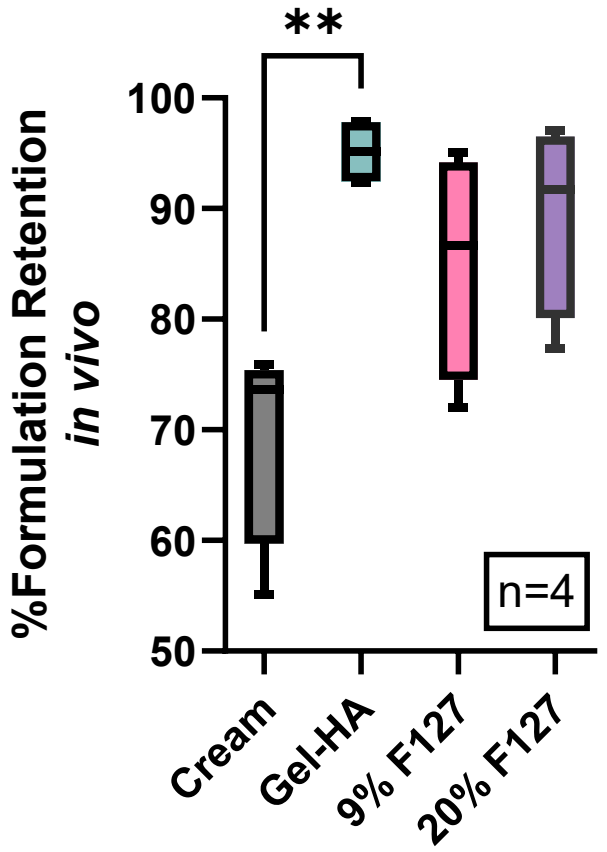




Hygroscopic – Can maintain moisture in the vagina to offer immediate relief of symptoms such as dryness and pain.

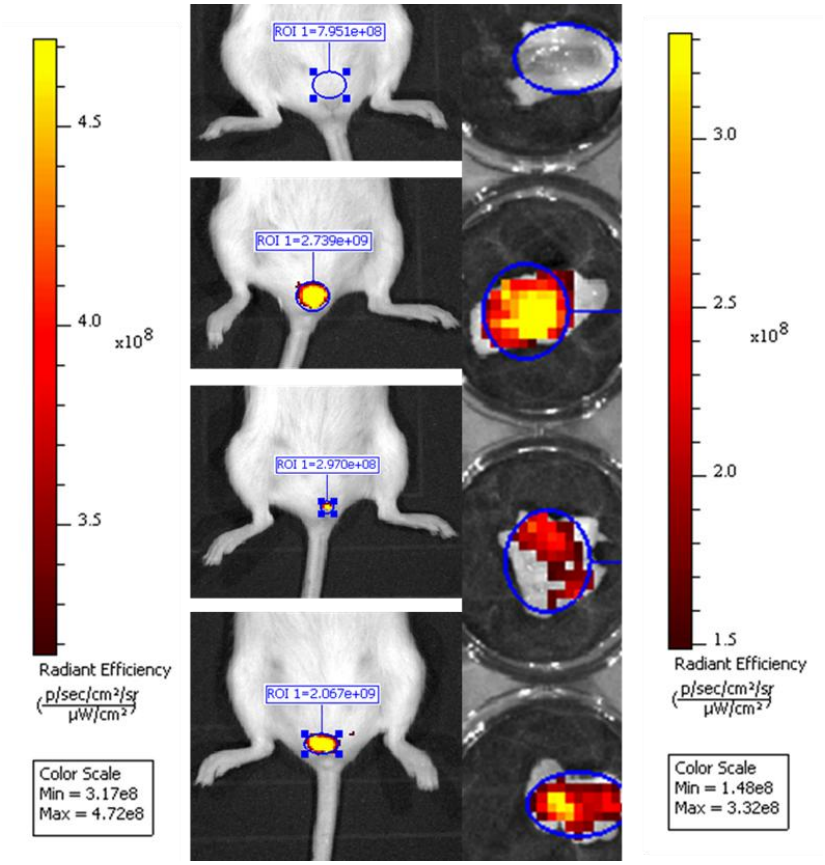
Gel retention in the reproductive tract

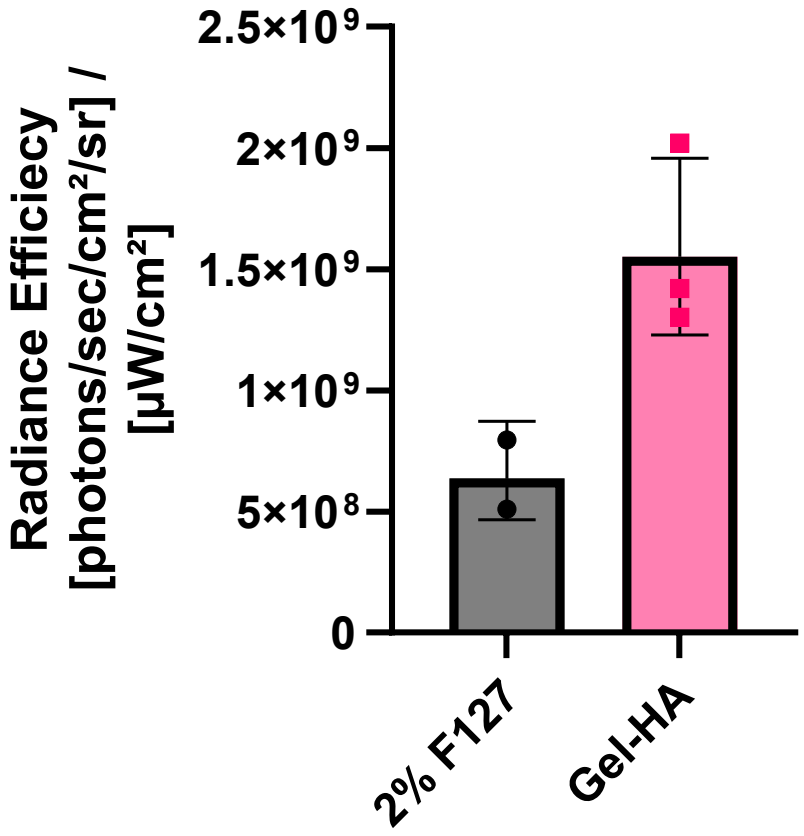




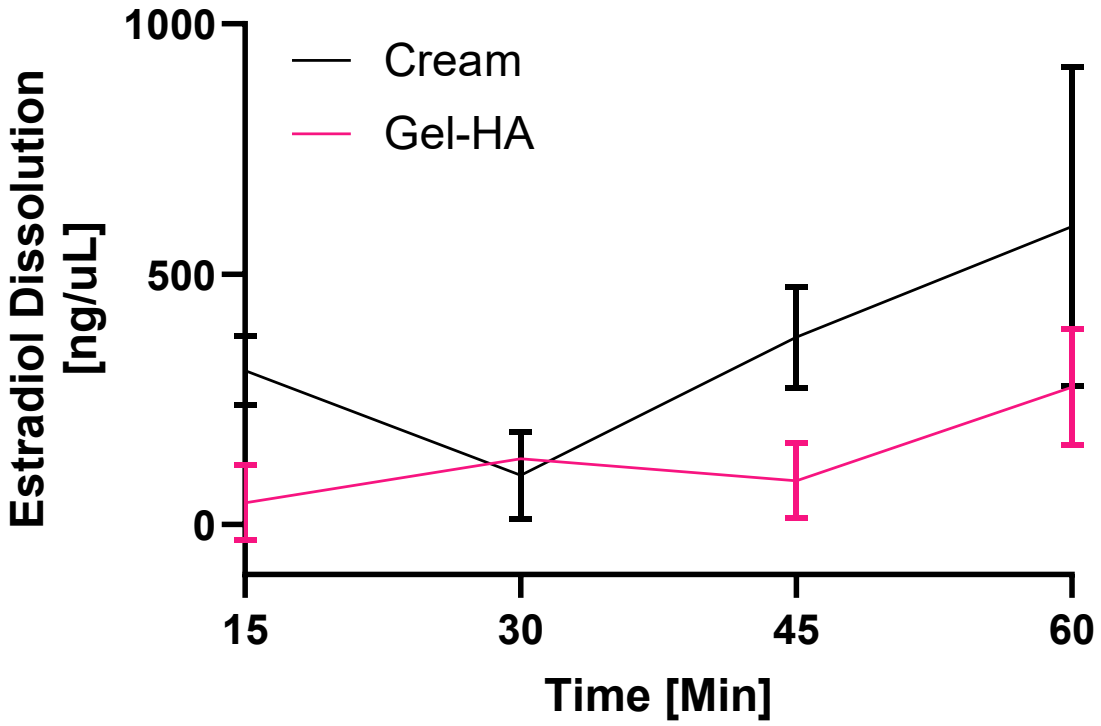
Shapiro *et al.*, Journal of Controlled Release, 2024

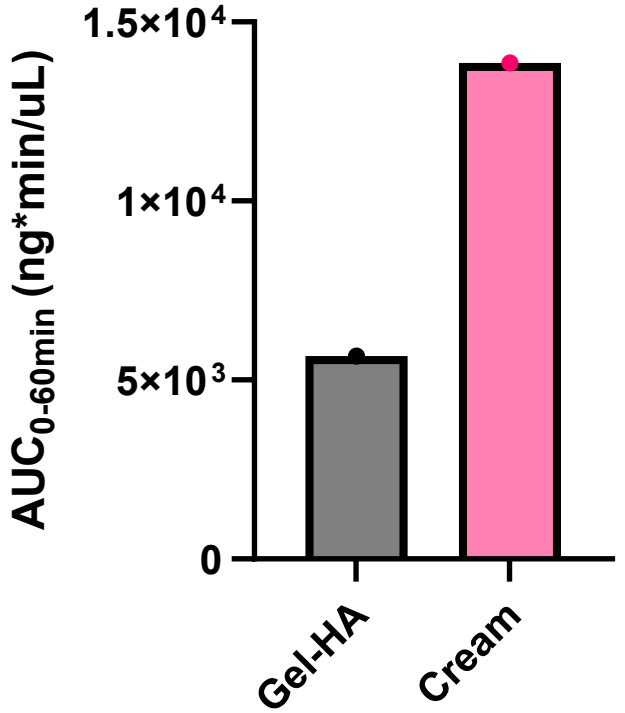
Rapid gel formation imaged 1 hr following vaginal administration



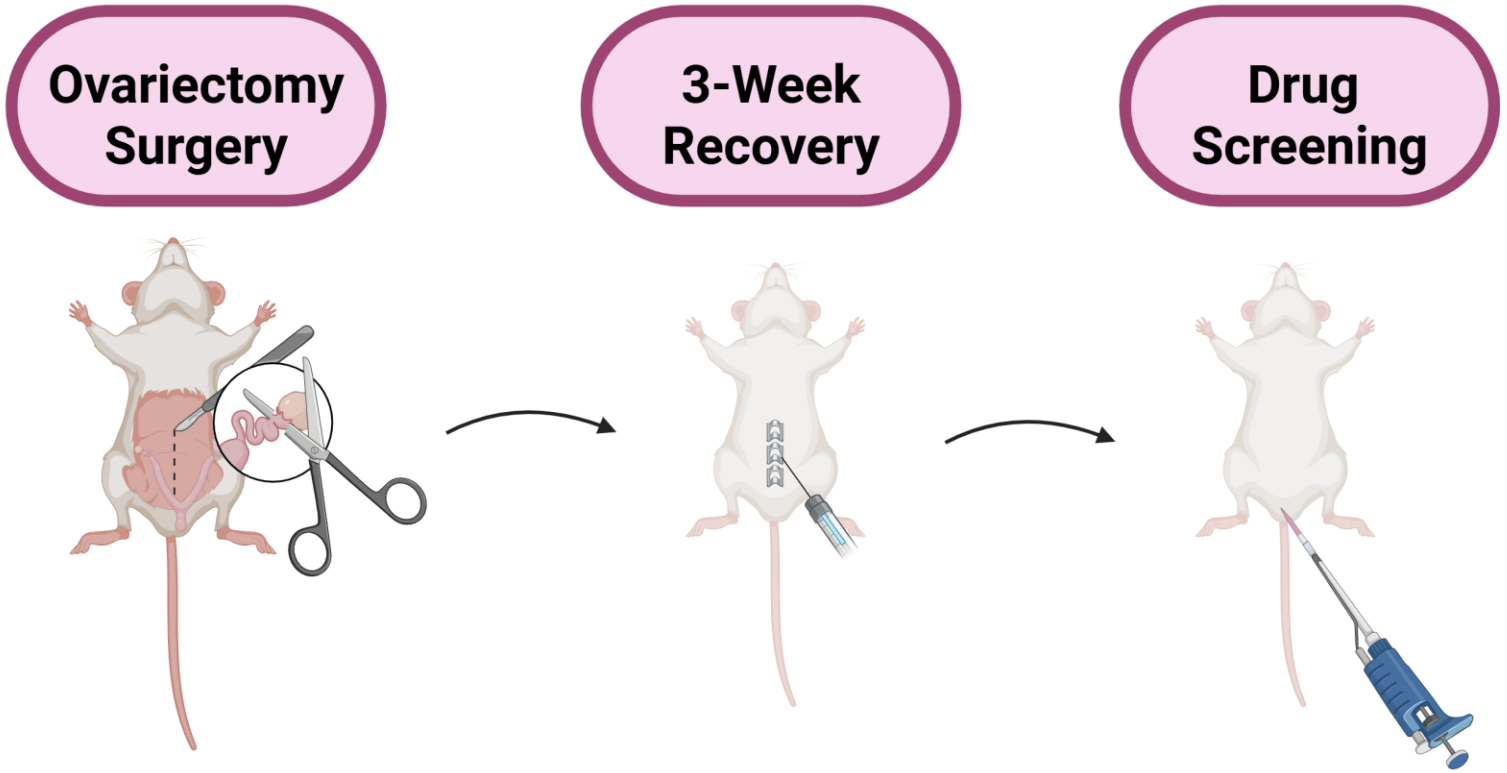


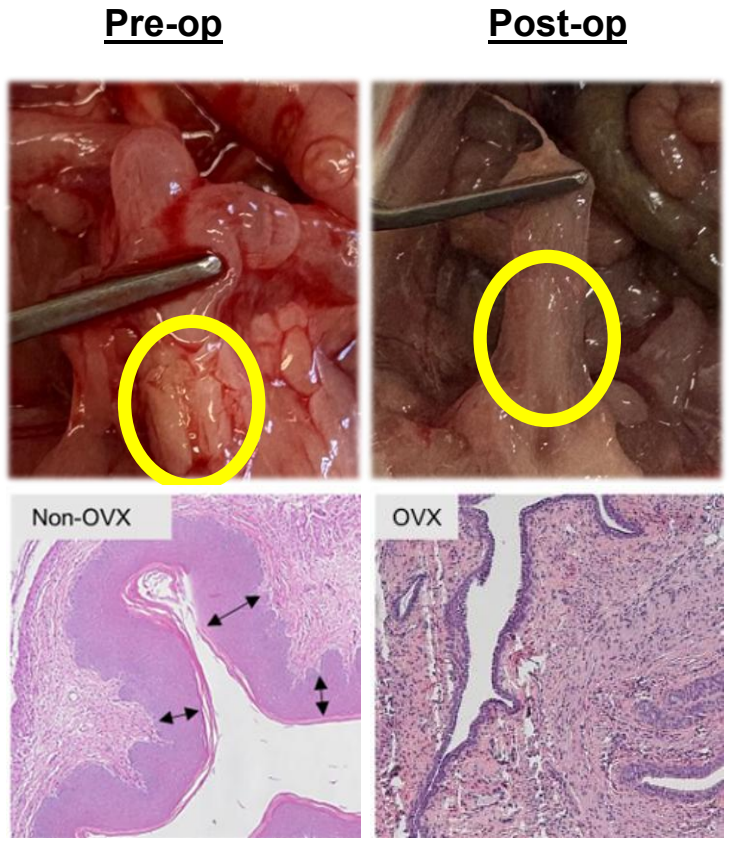
Timed drug dissolution from gel into simulated vaginal fluid appears lower compared to conventional therapy





Ongoing assessment of efficacy in mouse ovariectomized (OVX) menopause model





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Surgeries performed by Jairo Ortiz, M.D.

Conclusions

I. Rheological properties formulated at final *in vivo* concentration are favorable for vaginal drug delivery.
II. Hyaluronic acid improves retention and erosion, while it's hygroscopic properties may also serve to relieve immediate symptoms of VA.
III. Our selected vehicle formulation rapidly gels when formulated and delivered at half the expected in vivo concentration.
IV. Gel retention after 3 min in the FRT is significantly higher than conventional cream formulation.
V. Dissolution of 17-b estradiol over 1 hr is slower compared to conventional cream.

Ongoing and Future Work

- Assessment of drug release compared to commercial formulations *in vitro.*
- Preliminary PK Study on plasma and vaginal estradiol levels in OVX model 0-24 hours after dosing.
- 2- week treatment dosing gel formulation versus commercial cream every 3 days.
- Evaluate effects of formulation exposure on vaginal microbiota growth and local tissue inflammation.

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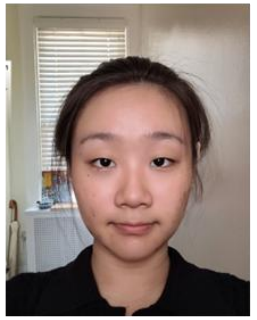

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