Computationally Guided Optimization of Next-Generation Selective Estrogen Receptor Modulators for Ovarian Cancer

Mehek Bapna[1], Akshat Gautam[1], MS, Arturo Orlacchio, Ph.D.[1], Emi Gacaj[1,2]

[1] Tessering Biosciences, [2] Columbia University in the City of New York

Background

Unmet Need

- Active duty women face disproportionate ovarian cancer burden at young ages: gynecologic cancer rates exceed the general population (49.17 vs 42.09 per 100,000), with a markedly higher ovarian-to-cervical ratio under age 45.[1]
- Over 300 active service members and 20,000+ DoD beneficiaries have been diagnosed with ovarian cancer in the past decade; most relapses are platinum-resistant, driving repeated hospitalizations.[2]
- DoD's universal-access system shows better 5-year survival than SEER, so treatment burden, not survival, is the key unmet need.[3]

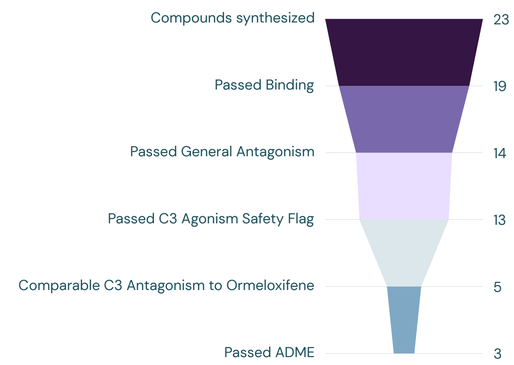
Promising Scaffold

- Ormeloxifene (ORM) is a third-generation selective estrogen receptor modulator originally developed and marketed in India as a once-weekly oral contraceptive, approved in 1991.
- ORM also demonstrates potent anti-tumor activity, inhibiting growth and inducing apoptosis across a panel of ovarian cancer cell lines, including cisplatin-sensitive (A2780), cisplatin-resistant (A2780-CP), and semi-resistant (SKOV-3) models.
- In a preclinical xenograft model of cisplatin-resistant ovarian cancer, ORM significantly reduced both tumor burden and peritoneal metastasis without apparent treatment-related toxicity.[4]
- In platinum-sensitive and -resistant models, ORM suppresses AKT signaling and disrupts cyclin/CDK activity (via p21, p27, cyclin D1/E, CDK2), driving G0/G1 arrest and apoptosis, including in p53-null cells, relevant given ~96% of high-grade serous ovarian cancers carry TP53 mutations.[4]

Our progress

Lead Optimization

Development of a focused library generating early structure–activity relationship (SAR), functional ER activity, and ADME data.



Translational Potential

Value to Military Healthcare Systems

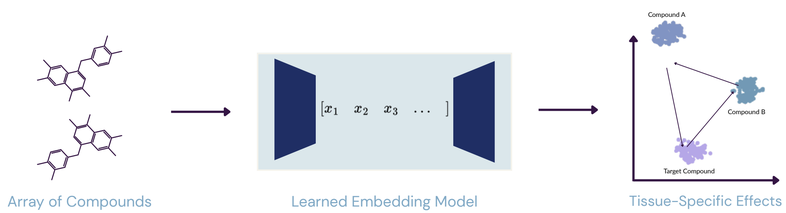
- An oral agent reduces per-patient costs associated with infusion center staffing, monitoring infrastructure, and treatment-related hospitalization, an efficiency relevant to DoD and VA healthcare budgets.
- Fewer hospitalizations and infusion visits directly preserve readiness for active-duty personnel and lower caregiver burden for the VA population.

Clinical Impact

- Potential to expand treatment options for patients with recurrent or platinum-resistant disease, including those with limited remaining treatment options.
- Potential to delay progression and reduce cumulative treatment burden in patients requiring repeated lines of therapy.
- Optionality for combination or maintenance regimens (alongside PARP inhibitors, immunotherapy, or as adjuvant therapy post-platinum)

Computational Platform

The ability to predict uterine agonism, a central and longstanding liability of SERMs, is highly relevant to drug development in this domain, especially within novel indications.



By coupling molecular dynamics with learned representations, we model tissue-specific entropic and conformational signatures to distinguish agonist from antagonist activity, enabling our optimization process to be more efficient and cost-effective.

Experimental assay data from our lead optimization provides supervision for simulation-derived representations, enabling predictive modeling.

Development Strategy

1. Profile the novel compound library across platinum-sensitive and platinum-resistant ovarian cancer models to establish activity, mechanism, and preliminary selectivity.
2. Advance prioritized leads into pharmacokinetic, tolerability, and efficacy studies, including platinum-resistant xenograft models, to support lead selection.
3. Nominate a development candidate and transition into CMC, GLP toxicology, safety pharmacology, and regulatory.

References

mehek@tesseringbiosciences.com