White Paper

Endometriosis: A complex therapeutic challenge

Advancing therapeutic innovation through targeted models for a multifactorial, estrogen-dependent disease with high clinical burden

Endometriosis affects 1 in 10 individuals with female reproductive anatomy, yet remains poorly understood, underdiagnosed, and undertreated.

Despite its chronic, estrogen-dependent, inflammatory nature and significant clinical burden, therapeutic innovation is strikingly limited, with fewer than 40 drugs in the global pipeline.

Disease overview

Etiophathogenesis and molecular characteristics

Ectopic endometrial lesions are histologically similar to eutopic endometrium but exhibit aberrant gene expression profiles, enhanced proliferative capacity, reduced apoptotic sensitivity, altered steroid receptor expression (e.g., ESR1, ESR2, PGR), and a proinflammatory cytokine milieu. The disease is estrogen-sensitive, with estradiol promoting survival, angiogenesis, neurogenesis, and immune evasion of lesions.

Several interrelated mechanisms have been implicated in pathogenesis:

Unmet needs in endometriosis

Endometriosis is a chronic, estrogen-dependent inflammatory disease defined by the ectopic implantation and proliferation of endometrial-like tissue outside the uterine cavity. It affects approximately 10% of individuals with female reproductive anatomy, with higher prevalence observed among those with infertility or chronic pelvic pain. Despite its widespread incidence, the pathogenesis remains incompletely elucidated, diagnostic latency is substantial (average 7–10 years), and therapeutic interventions are largely empirical and non-curative.

Although endometriosis affects such a significant portion of the global population, fewer than 40 drugs are currently in preclinical development or clinical trials worldwide targeting this condition.

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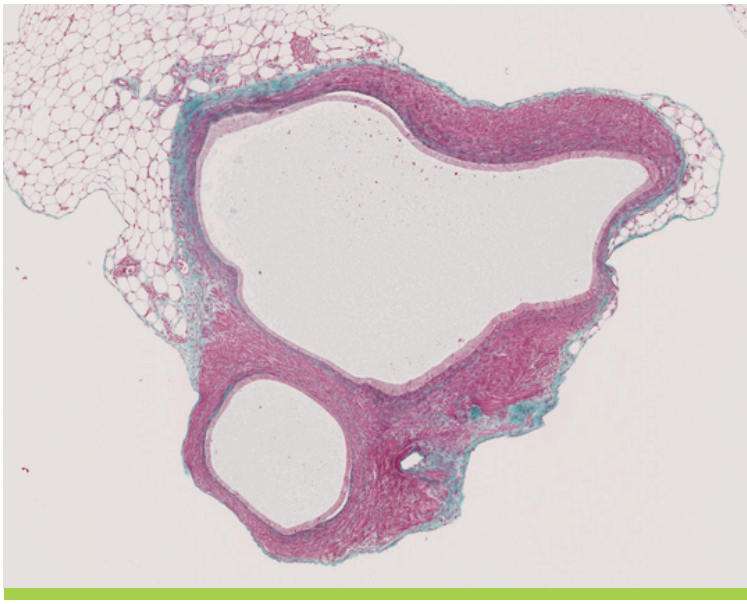
- Retrograde menstruation and peritoneal implantation, though nearly ubiquitous in menstruating individuals, does not alone explain disease susceptibility.
- Coelomic epithelium (that normally lines the surface of the body wall and abdominal organs) metaplasia and embryonic Müllerian duct remnants offer plausible explanations for extrapelvic disease.
- Bone marrow-derived stem/progenitor cell recruitment may contribute to lesion initiation.
- Impaired immune surveillance, particularly involving macrophages, NK cells, and dendritic cells, is a hallmark of lesion persistence.
- Genetic and epigenetic alterations, including polymorphisms in WNT4, VEZT, and GREB1, modulate risk.
- Epigenomic dysregulation affects DNA methylation and histone modifications, contributing to aberrant gene expression and progesterone resistance.

Clinical phenotypes and symptomatology

Endometriosis presents along a spectrum from asymptomatic to severely symptomatic, with clinical subtypes including superficial peritoneal lesions, ovarian endometriomas, and deep infiltrating endometriosis (DIE). Symptomatology is highly heterogeneous and may include:

- Severe dysmenorrhea
- Non-menstrual pelvic pain
- Dyspareunia
- Dyschezia and dysuria
- Chronic fatigue
- Subfertility / infertility

The symptom burden correlates poorly with lesion burden, complicating clinical assessment and highlighting the neuroimmune dimensions of disease progression, including peripheral and central sensitization.



Above: Cystic lesion in pelvic adipose tissue, consisting of endometrium and myometrium – murine model of endometriosis – Masson's trichrome.

Diagnostic paradigms and limitations

Definitive diagnosis currently relies on laparoscopic visualization and histopathological confirmation, despite efforts to validate non-invasive modalities. Imaging techniques such as transvaginal ultrasound and MRI are limited by operator expertise and resolution constraints, particularly for superficial or DIE lesions. There is an urgent unmet need for circulating biomarkers (e.g., microRNAs, cytokines, glycoproteins) with sufficient sensitivity and specificity to enable early, non-invasive diagnosis and longitudinal disease monitoring.

Unmet need and therapeutic strategy

Current treatment paradigms are palliative and predominantly aimed at suppressing ovulatory cycles, reducing estrogen signaling, and alleviating pain:

- Hormonal suppression (e.g., GnRH analogs, progestins, combined oral contraceptives)
- NSAIDs for symptomatic pain relief
- Surgical excision, often followed by pharmacologic suppression to reduce recurrence
- Emerging therapies, including selective progesterone receptor modulators (SPRMs), aromatase inhibitors, and non-hormonal targets (e.g., IL-1β, TNF-α, angiogenesis inhibitors), are under preclinical or early clinical evaluation

Long-term hormonal therapy is constrained by side effects and contraindications, particularly in individuals seeking fertility. Surgical outcomes are variable and frequently associated with disease recurrence and morbidity. Thus, there is a pressing need for mechanism-based therapeutic development supported by robust preclinical models.

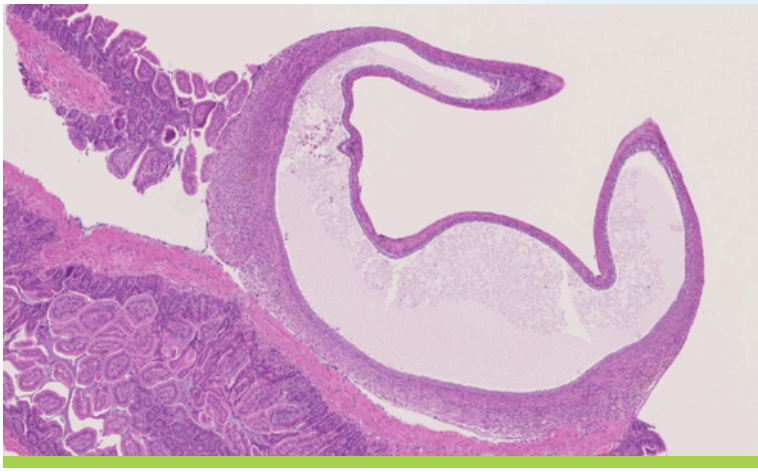
Preclinical models

Diagnostic paradigms and limitations

Strategic use of animal models still plays a key role in elucidating disease mechanisms and conducting early-stage therapeutic evaluation. Critical factors for model utility include fidelity to human lesion biology, hormonal responsiveness, immune context, and quantifiable endpoints. Existing rodent models can be categorized as:

- Autologous transplantation models (e.g., uterine fragment implantation in syngeneic hosts)
- Xenograft models, involving transplantation of human endometrial tissue into immunodeficient mice
- Genetic models, although limited in endometriosis research due to lack of lesion specificity

To most effectively support endometriosis-related therapeutic development, our validated murine models replicate critical features of human disease, including lesion vascularization, macrophage infiltration, and nociceptive sensitization. These platforms enable evaluation of both molecular mechanisms (e.g. ER/PR signaling, inflammatory cascades) and pharmacological interventions in a physiologically relevant context.



Above: Cystic lesion on intestine, consisting of endometrium and myometrium – murine model of endometriosis – H&E stain.

- Establishment of supply chain for patient derived lesions
- Target validation : gene expression (qRT-PCR, in situ hybridization) or protein quantification in lesions (ELISA, Western Blot)
- In vivo murine models: preclinical compound testing (lesion development, fibrosis, pain, hormonal sensitivity...)

Partnering toward innovation

As research shifts toward a systems-level understanding of endometriosis—integrating hormonal, immune, neural, and genetic axes—robust preclinical systems are imperative. Oncodesign Services offers translational in vivo platforms tailored for pharmacodynamic studies, dose optimization, and biomarker validation.

We welcome collaboration with academic, biotech, and pharmaceutical partners engaged in the discovery and development of next-generation therapeutics for endometriosis. Our commitment is to facilitate innovation that transcends symptomatic relief and addresses the underlying pathobiology of this debilitating disorder.

Next steps

To learn more about our endometriosis models and preclinical development facilities, contact us today.

Reach out to your relationship manager or contact us at:

- **oncodesign-services.com**
- **contact@oncodesign-services.com**

More information

Oncodesign Services is a leading CRO specializing in drug discovery and preclinical services. Our mission is to help researchers discover innovative therapies against cancers and serious diseases with high medical need. We have been performing translational science for over 30 years, providing the partnership required to help our clients progress from therapeutic target to advanceable preclinical candidates.

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