

Treating endometriosis

By using a tissue-specific hormone inhibitor to rebalance local estrogen metabolism, Forendo Pharma could provide long-term treatment to millions of women suffering from endometriosis.

With its expertise in tissue-specific hormone therapies, the Finnish company Forendo Pharma is tackling endometriosis, a condition that affects 10% of women of childbearing age. "Endometriosis is a difficult condition to treat, mainly because the estrogen-deficiency symptoms generated by the currently used drugs prevent long-term use. Unlike these therapies, our strategy uses novel 17- β -hydroxysteroid dehydrogenase (HSD17B) inhibitors which act locally, without impacting the systemic estrogen level," said company CEO Risto Lammintausta.

The company was founded in 2013 by Finnish drug development pioneers to exploit the findings of leading endocrinology researchers Matti Poutanen and Antti Perheentupa, from the University of Turku and Turku University Hospital, Finland. Led by Lammintausta, who has over 30 years of experience in pharmaceutical R&D, and with substantial international investment from funds including Novo Seeds, Karolinska Development, Novartis Venture Fund, Merck Ventures and Innovestor, the company is growing and expects its first endometriosis drug to enter clinical development in 2018.

Endometriosis occurs when endometrial tissue, normally formed in the lining of the uterus, starts to grow outside the uterine cavity, creating endometriotic lesions. This can lead to painful periods and ovulation, pain during or after sexual intercourse, abnormal bleeding, chronic pelvic pain, fatigue and infertility. There is no known cure for the condition, which is estimated to affect 170 million women and teen girls.

"Efficient drug treatments are currently based on suppression of ovarian estrogen synthesis or antagonizing estrogen action," explained Poutanen. "These systemic therapies lead to estrogen deprivation but often offer only modest efficacy. They also have harmful safety profiles, and can cause loss of bone density and several menopause-like side effects that preclude long-term use."

Endometriosis development candidate

Forendo Pharma has developed a novel clinical candidate compound that blocks the formation of high levels of the potent estrogen estradiol, which is responsible for the proliferation of endometriotic lesions and contributes to pain. Most important, it does this without affecting ovarian hormone production. The concept, developed together with the University of Turku scientists, is based on the previously unexploited drug target HSD17B1.

The endometriotic tissue of women with endometriosis shows high estrogen levels. The enzyme HSD17B1 is part of the mechanism that regulates

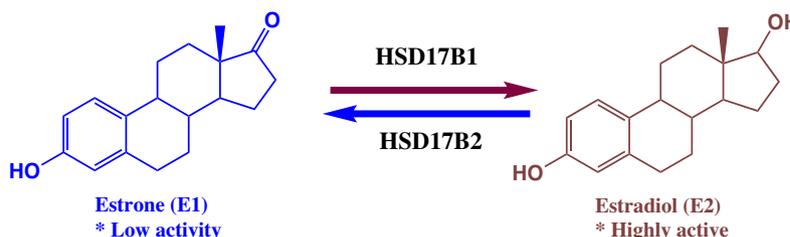


Figure 1: Forendo's FOR-6219. The basic concept behind the HSD17B1 inhibitor involves blockage of the conversion of estrone to estradiol.

estrogen action, by converting non-active estrone into active estradiol within endometrial cells. When this pathway is blocked, the build-up of high levels of the estrogenic hormone estradiol is prevented, which will limit the ability of endometrial cells to form endometriotic lesions.

"Using HSD17B1 inhibitors we have shown that we can inhibit estradiol production inside human endometriosis samples *ex vivo*," explained Lammintausta. Forendo's potent and selective lead compounds have also demonstrated *in vivo* proof of efficacy in a primate disease model of endometriosis.

Novel inhibition of HSD17B1 offers great promise in this field, which has significant morbidity and unmet clinical needs

Linda Giudice, professor of obstetrics, gynecology and reproductive sciences, University of California

There are potentially multiple benefits to this inhibition, including reduced endometrial cell proliferation and diminished inflammation, but one of the biggest advantages will be the reduction in off-target effects. "Selectivity is a critical feature, and inhibiting the local estradiol production with HSD17B1 inhibitors is likely to have long-term tolerability, providing a long-term treatment option for the often young and active women who suffer from the condition," Lammintausta added.

Part of the problem with the disease has been the delay in diagnosis and treatment, which leads to further complications and often means that the disease has progressed. In such cases the patient may present with infertility symptoms or chronic pain that

cannot be controlled with hormonal therapies or even surgery. "Whilst more efficient tools for diagnosis also need to be developed in order to provide an opportunity to treat women at an earlier stage and prevent these problems, HSD17B1 inhibitors offer a treatment option that could be offered before reaching these stages," said Perheentupa.

"Effective therapies for relief of endometriosis-associated pain that have minimal side effects comprise the 'holy grail' of endometriosis management as stand-alone approaches or adjunctively with surgery. Novel inhibition of HSD17B1 offers great promise in this field, which has significant morbidity and unmet clinical needs in those affected," said Linda Giudice, professor of obstetrics, gynecology and reproductive sciences at the University of California, San Francisco, and chair of Forendo's Advisory Board.

Forendo Pharma's HSD17B1-inhibitor drug candidate, FOR-6219, is now progressing into clinical development. The company plans to take the drug through clinical proof of concept before partnering for further development stages. Forendo's pipeline also includes fispemifene, a selective estrogen-receptor modulator that is a phase 2 asset for the treatment of male urological conditions. The company is open to opportunities to use its expertise in tissue-specific hormone mechanisms for other applications and in 2018 will seek series B funding to broaden its women's health pipeline. "With our tissue-specific hormone therapeutics approach, Forendo is well placed to make a real difference to women's health in the near future, and we look forward to working with partners to make this happen," said Lammintausta.

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