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selective 17βHSD1 inhibitors

https://www.iocbtech.cz/project/selective-17%ce%b2hsd1-inhibitors/

Scientists

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CHALLENGE

17βHSD1 an enzyme that has been known to play a pivotal role in tissue specific estradiol (E2) synthesis for more than fifty years. E2 is a very potent hormone, which regulates the expression of a variety of genes by binding to estrogen receptors (ER) and thus it plays a crucial role in the physiological as well as pathological proliferation and differentiation of the target cell. 17βHSD1 affects breast cancer cell proteome and modulates expression of several genes at both mRNA and protein levels. Furthermore, it is associated with an increased risk of cell migration and cancer relapse. Therefore, regulation of 17βHSD1 should be considered as potential novel endocrine therapy or 17βHSD1 expression as an independent prognostic marker in breast cancer patients. Higher expression levels of 17βHSD1 have been observed in non-small-cell lung carcinoma (NSCLC) Furthermore, significant high E2 levels are described in endometriosis, uterine leiomyomas (fibroids or myomas), adenomyosis, menorrhagia, and dysmenorrhea. At present, no 17βHSD1 inhibitor has reached clinical trials.

TECHNOLOGY

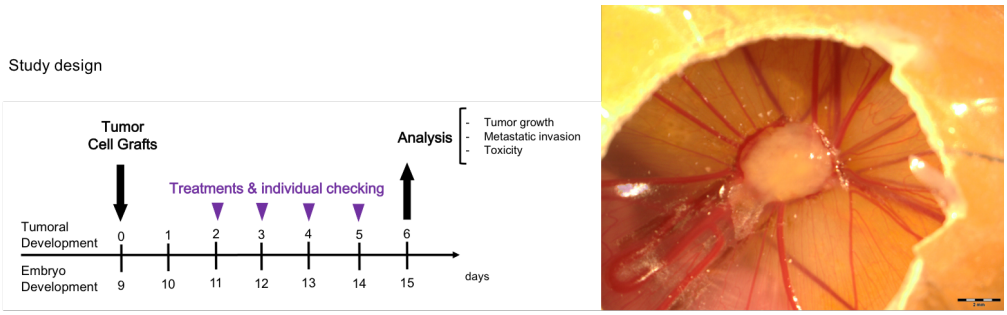
We have successfully developed highly potent and specific inhibitors of 17βHSD1. We have recently shown the efficacy of these compounds in *in vitro* and *in vivo* testing of E1 to E2 conversion after application of the lead compound.

Proof of concept experiments:

- No significant toxic effect shown in *vitro* and *vivo*
- Experiments on T47D cells show inhibition of 17βHSD1(accumulation of E1 in HPLC MS/MS detectable)
- Proof of concept experiments in egg-disease models

The objective of this study was to test the concept of inhibiting 17βHSD1 and its effect on T47D breast carcinoma cells as well as the efficacy of our lead compound **EP449.** The test was performed on an egg model developed by INOVOTION. At day 16 of the egg embryonal development, following 4 treatments (at day 2, 3, 4 and 5 after grafting), tumors were collected, fixed, cleaned and weighted: at the dose tested (50 µmol.l-1) **EP449** had the same effect as 4-hydoxytamoxifen, used as positive control (200 µmol.l-1), showing a 12-13 % reduction, both compounds showed a reduction of metastasis.

In terms of toxicity, the same ratio of dead/alive eggs between groups was observed, even in the negative control group. No specific toxicity of **EP449** was proven.



Engrafted T47D cells

COMMERCIAL OPPORTUNITY

The technology is offered for co-development and licensing.

DEVELOPMENT STATUS

Early preclinical stage, in vitro and in vivo testing, lead optimization, toxicology.

PATENT SITUATION

Patent application in international (PCT) phase with priority date in June 2016

IP OWNERS

- Institute of Organic Chemistry and Biochemistry AS CR, v.v.i., Prague, Czech Republic
- Institute of Molecular Genetics AS CR, v.v.i. , Prague Czech Republic
- Institute of Molecular and Translational Medicine, Olomouc Czech Republic
- Helmholtz Zentrum München, Germany

FURTHER READING