HHS Public Access

Author manuscript

*Gene*. Author manuscript; available in PMC 2019 July 23.

Published in final edited form as:

*Gene*. 2016 August 15; 588(1): 54–61. doi:10.1016/j.gene.2016.04.031.

# Current knowledge of the multifunctional 17β-hydroxysteroid dehydrogenase type 1 (HSD17B1)

**Wanhong He**[a], **Misra Gauri**[b], **Tang Li**[c], **Ruixuan Wang**[c], **Sheng-Xiang Lin**[a,c]

[a]Shanghai Engineering Research Center of Reproductive Health Drug and devices, Shanghai 200032, China

[b]Amity Institute of Biotechnology, Amity University, Noida, U.P. (India)

[c]Laboratory of Endocrinology and Oncology. CHU Hospital Center Research Center and Laval University

## 1. The origin and evolution of the 17β-HSD1 gene (HSD17B1)

As early as the late 1940s and early 1950s, an enzyme regulating the balance between estrone (E1) and estradiol (E2) was discovered in human placenta (Langer & Engel, 1958). Enzyme activity in both prokaryotic and eukaryotic species was described about this first discovered member of the 17β-hydroxysteroid dehydrogenase family, *i.e.* 17β-HSD1. During the course of evolution, genes encoding the 17β-HSD enzymes developed individually approximately 540 million years ago parallel to those for steroid receptors (Baker, 2004; Jansson, 2009). This implies an important evolutionary role for the 17β-HSD enzyme family.

Human 17β-HSD1 was the first 17β-HSD to be cloned and sequence identified (Luu-The et al., 1989; Peltoketo et al., 1988). Its three-dimensional structure is also the first example of any human steroid-converting enzyme (Ghosh et al. 1995; Azzi et al. 1996; Lin et al., 1996). The 17β-HSD1 gene was determined to be located in the q.12.1 band of chromosome 17 through gene mapping by *in situ* hybridization. This enzyme contains 327 amino acids and exists as a homodimer with two identical subunits of 34.5 kDa (Lin et al., 1992; Peltoketo et al., 1988). 17β-HSD1 uses NADPH as a co-factor to catalyze the conversion of E1 to E2, and to a minor extent that of androgens such as 4-androstenedione (4-Adione) to testosterone (T) (Lukacik et al., 2006). 17β-HSD1 can bind to both triphosphate cofactors (NADPH) and NAD (H) at the molecular level but with much higher specificity to the former, which is rich in cells that largely governs the enzyme's catalytic direction towards estrone reduction (Karavolas et al., 1970; Lin et al. 1992; Sherbet et al., 2007). Enzyme kinetics and X-ray crystallographic studies have shown that 17β-HSD1 has the potential to bind C-19 steroids in both normal and reverse orientations resulting in the 3β-reduction of DHT into 5-androstane-3,17-diol (3β-diol) and 17β-oxidation of DHT into A-dione, both

leading to the inactivation of the most potent androgen DHT (Gangloff et al., 2003). 17β-HSD1 expression positively correlates to estrone activation, E2 levels, and proliferation of breast cancer cells (Aka et al., 2010). The multi-specificity of 17β-HSD1 is structurally based on the pseudo-symmetric structures of androgens that can accommodate the narrow enzyme substrate tunnel by both normal and alternative binding (Lin et al., 2013). Thus, 17β-HSD1 up-regulates breast cancer cell growth by a combined action on estradiol synthesis and DHT inactivation.

In primates, 17β-HSD1 is primarily expressed in the placenta and ovarian granulosa cells and to a lesser extent in the endometrium, adipose tissue and prostate. It is not expressed in the testes or adrenals (Schwabe et al., 2001; Takeyama et al., 2000). This tissue-specific expression makes 17β-HSD1 an attractive pharmaceutical target in women's diseases (Lukacik et al., 2006), particularly the breast cancer. Today, fifteen 17β-HSD enzymes have been discovered in mammals and the nomenclature of these enzymes follow their discovery order. All of these belong to the short-chain dehydrogenase/reductase family (SDR) with the exception of 17β-HSD5, which is an aldo-keto-reductase (AKR). Short-chain dehydrogenase/reductase enzymes are multimeric in nature, expressed in a variety of organisms with NADPH as co-factor. Aldo-keto-reductase enzymes act as monomers and also use NADPH as co-factor. A high degree of substrate variability is shown by SDR enzymes including: steroids, retinoids, fatty acids and prostaglandins. 17β-HSD enzymes are localized in different parts of the cell across diverse tissues and show preference for a variety of substrates and co-factors. A feature common to all 17β-HSD enzymes is the ability to catalyze oxidation or reduction of the carbon at position 17 in the steroids. These enzymes have different substrate preferences such as E1, E2, T, 3beta-diol and DHT. They possess distinct physiological functions (Jansson, 2009).

## 2. Comparison of particular gene expression in different organisms, animals and human

The sequence identities between human 17β-HSD1 and other species range from 51% (zebra fish) to 99% (chimpanzee) and homologies range from 70% to 100%, respectively. The biggest differences are located in the F/G segment (residues191–230), which lines the hydrophobic substrate binding site (SUB) and in the C-terminal region (Miyoshi et al., 2001).

Human 17β-HSD1 catalyzes the reduction of the weak estrogen E1 to the most potent, E2. This occurs in target cells where the estrogenic effect is exerted *via* the estrogen receptor (ER). Estrogens, especially E2, are known to stimulate the proliferation of hormone-dependent diseases (Chetrite GS., 2005) such as breast cancer. The risk of breast cancer is positively correlated with a high level of E2 (Pasqualini et al., 1996), because this potent estrogen plays an important role in the proliferation of cancer cells (Castoria et al., 2010). It has been confirmed by microarray analysis that E2 regulates estrogen response elements (EREs), progesterone receptor (PR), pS2 and cathepsin D that affects the cell growth and differentiation (Laganière et al., 2005; Cicatiello et al., 2004).

The majority of breast cancer tumors (60–80%) express high levels of ERs, which accounts for the proliferative effect of estrogens. They tend to have a higher intratumoral estrogen concentration in comparison to normal breast tissue and plasma (Labrie et al., 2000). There is a direct relation between high [E2]/[E1] ratio and breast cancer cell proliferation. Strategies targeting the reduction of [E2]/ [E1] ratio, are proposed to be an effective means of facilitating breast cancer therapy (Zhang et al., 2012). *In situ* synthesis and metabolism of estrogens is believed to be of great importance for the development and progression of breast cancer. In fact, 17β-HSD1 is overexpressed in many breast tumors and as such it is an attractive target for the treatment of these diseases (Frotscher et al., 2008).

In accord with its role in sex-hormone signaling, 17β-HSD1 is expressed in placenta, endometrium and ectopic pregnancy. Immunohistochemical assays revealed that 17β-HSD1 is present in syncytiotrophoblast (ST) cells (Li et al., 2005), a large portion of extravillous cytotrophoblast (EVCT) cells and 20% of column cytotrophoblast (CCT) cells. On the other hand, no expression of 17β-HSD1 was detected in villous cytotrophoblast (VCT) cells. Localization of 17β-HSD1 was found on the surface of glandular epithelial cells when progesterone was present at typical ovulatory cycle concentrations (Mäentausta et al., 1991). It was also associated with endometrial carcinoma. In addition, 17β-HSD1 is found in epithelial cells of the fallopian tube. Interestingly, the expression level of 17β-HSD1 in the fallopian tube epithelium during tubal pregnancy is significantly higher than that found during a normal cycle. There is evidence that normal and tubal pregnancies possess identical expression of P450 aromatase and 17β-HSD1 in ST cells implicating similar E2 production in the placenta (Li et al., 2003). Furthermore, the association of 17β-HSD1 with EVCT cells indicates that 17β-HSD1 perhaps plays a role in trophoblast invasion. Increased expression of 17β-HSD1 in the epithelial cells of the fallopian tube may lead to a local E2 supply sufficient for the maintenance of tubal pregnancy (Li et al., 2003). The synthesis of estrogens was recently demonstrated in non-small cell lung carcinomas (NSCLCs) *via* aromatase activity. Moreover, an aromatase inhibitor (AI) did suppress estrogen receptor-positive NSCLC growth (Hershberger et al., 2005; Verma et al., 2011). Recent studies highlights the importance of 17β-HSD1 as an important prognostic factor in NSCLC patients making it an attractive target that can improve the clinical response in estrogen-responsive NSCLC patients (Verma et al., 2013).

## 3. Structure–biological functions: dual estrogen and androgen activities and disease implications

The homogeneity and high activity of the enzyme preparation developed in early 1990s, significantly improved from former purifications, laid down the enzyme's crystallization and structural determination as the first human steroid-converting enzyme (Lin et al. 1992; Zhu et al. 1993; Ghosh et al. 1995a, 1995b). It has been elucidated by structural and mutagenesis studies that in the Rossmann fold (Breton et al., 1996; Buehner et al., 1973) of 17β-HSD1, a positively charged amino acid is able to form a salt bridge with the 2′-phosphate group of the cofactor NADP(H), *i.e.* Arg37 in 17β-HSD1 (Huang et al., 2001). Structural analysis, mutagenesis studies and sequence alignment have resulted in the identification of features essential for the catalytic process namely three conserved amino acid residues, Ser142,

Tyr155 and Lys159 constituting a “catalytic triad” with a water molecule (Puranen et al., 1994, Ghosh et al. 1995). Further investigations showed that an additional conserved water molecule stabilized by an H-bond interaction with an Asn114 residue (together with the “catalytic triad” to form a “catalytic tetrad”) plays a critical role in the enzymatic process for HSDs (Filling et al., 2002; Hwang et al., 2005). Three catalytic mechanisms are proposed for 17β-HSD1 (Ghosh et al. 1995; Ghosh & Vihko, 2001; Penning, 1997): one concerted (simultaneous transfer of hydride and proton, not shown) and two stepwise. The latter differs in the intermediate presence of either an oxyanion or a carbocation. (A) Firstly, the pro-S hydride of NADPH is transferred to the α-face of E1 at the planar C17 carbon resulting in an energetically favorable aromatic system; the resultant oxyanion is subsequently protonated by the acidic -OH group of Tyr155 (A2). (B) In the second proposed mechanism, initially the keto oxygen of E1 is protonated by the acidic -OH of Tyr155; the resultant carbocation then accepts the pro-S hydride of NADPH at the α-face. The proton relay is facilitated by a H-bond network involving Lys159, two water molecules and Asn114, an electrostatic interaction between the protonated side chain of Lys159 and the phenyl ring of Tyr155 (Ghosh et al. 1995; Ghosh & Vihko, 2001) as well as T-stacking between Phe192 and Tyr155 (Negri et al., 2010). Hydrogen bonds are represented by dashed lines in Figure 1 and π–π-interactions are not depicted for the sake of clarity. Despite the availability of enormous structural information, the most likely mechanism is highly debated (Marchais-Oberwinkler et al., 2011).

To date, 20 crystal structure forms of 17β-HSD1 are available in the protein data bank (PDB) as: apo-enzyme (1bhs), holo-enzyme (1fdv, 1qyv), binary complex with E2, androgens or inhibitors (1fds, 1fdw, 1dht,3dhe, 1jtv, 1iol, 3dey, 1i5r, 3hb4, 3klm) and ternary complex with cofactor and E2 or inhibitors (1fdt, 1equ, 1fdu, 1a27, 1qyw, 1qyx,3hb5). Remarkably, no crystal structure has been determined with the E1 substrate (Marchais-Oberwinkler et al., 2011).

All crystals reveal an overall identical tertiary structure: a rigid cofactor binding site (COF) and a narrow, hydrophobic SUB, which constitutes a “substrate recognition domain” delimited by the C-terminal region (Alho-Richmond et al., 2006; Azzi et al., 1996). Estradiol is stabilized by hydrogen bonds between the O3 and His221/ Glu282, as well as between the O17 and Tyr155/ Ser142 (Azzi et al., 1996). Flexible βFαG′ loop accounts for the major differences in the structures. This loop is not resolved in twelve crystal structures and can occupy three possible orientations depending on the presence of cofactor and ligands: an opened, a semi-opened and a closed enzyme conformation (Negri et al., 2010). The binding mode is known for some steroidal inhibitors as they have been co-crystallized in complex with 17β-HSD1 (1equ, 3hb5, 1i5r). The data revealed the importance of a defined βFαG′ loop conformation for compound binding. Since no protein structure complex with non-steroidal inhibitors exists, computational studies have been performed to investigate their binding. These studies showed that the choice of the crystal structure was the determinant for the identification of a binding mode and that the latter was strongly dependent on the loop conformation (Bey et al., 2009). The multi-specificity of the enzyme has been studied and reviewed (Lin et al. 1999). The cofactor hydrogen bonding onto the enzyme main chain was found to be conserved in 17β-HSD1 as well as in other short-chain

dehydrogenase/reductase family and contributes to nicotinamide orientation (Shi & Lin, 2004).

Two principal pathways are implicated in the final steps of E2 activation in breast cancer tissue. The aromatase pathway transforms androgens into estrogens (Batzl et al., 1996), the sulfatase pathway converts DHEA sulfate into DHEA and estrone sulfate (E1S) into E1 (MacIndoe, 1988; Pasqualini et al., 1989), followed by E1 conversion into the potent E2 by the action of reductive 17β-HSDs (Aka et al., 2009; Nguyen et al., 1995; Pasqualini, 2004, Lin et al. 2010). Quantitative evaluation indicates that in human breast tumors, DHEAS and E1S *via* sulfatase is a much more likely precursor for E2 than androgens *via* aromatase (Santner et al., 1984). 17β-HSD1 remains an important enzyme for E2 production because it can use E1 as substrate for both aromatase and sulfatase pathways with NADPH as cofactor (Nguyen et al., 1995; Poutanen et al., 1995). Moreover, the expression and activity of 17β-HSD1 are significantly higher in breast cancer than in normal breast tissue (Pasqualini, 2004) and it has been suggested that this higher expression could explain the elevated E2 concentration in breast tumors. 17β-HSD1 is a major player for E1–E2 conversion and cell viability in estrogen-dependent breast cancer cells, particularly in the T47D cell line (Zhang et al., 2014). Epidemiological evidence indicates that most breast cancer risk factors are associated with prolonged exposure of the mammary gland to high levels of estradiol (E2). This potent estrogen plays a crucial role in the development and evolution of hormone-dependent breast cancer. Approximately 60% of premenopausal and 75% of postmenopausal breast cancer patients is hormone dependent (Aka et al., 2012).

17β-HSD1/ DHT complex crystals were obtained by soaking the apo-enzyme crystals and the complex formation was confirmed after structure determination. The complex structure was solved at 1.7 Å resolution (Aka et al., 2010). Stereo representation showed the H-bond of DHT with the residues His221 in the reverse binding mode, whereas the normal binding mode lacks this H-bond interaction. Distances between DHT, Tyr155 and the cofactor NADP are different. In the reverse mode, the distance between the O3 of DHT and NC4 of NADP is 4.35 Å and between Tyr155 to NC4 of NADP is 5.4 Å whereas in the normal mode, the distance between the O17 of DHT and NC4 of NADP is 3.75 Å and between Tyr155 to NC4 of NADP is 5.4 Å (Fig.2). The reduction of DHT into both 3β-diol and 3α-diol by 17β-HSD1 points towards the potential of DHT binding to the enzyme in two orientations. These results strongly support the rationale for inhibiting 17β-HSD1 in breast cancer therapy to eliminate estrogen activation *via* the sulfatase pathway while avoiding the deprivation of DHT (Aka et al., 2010). It was recently found that 17β-HSD1 increases breast cancer cell migration in spite of its positive regulation of the anti-metastatic gene nm23. This also correlates with its capacity to stimulate breast cancer cell growth, further confirming the necessity of targeting this enzyme in ER-positive breast cancer. These novel findings suggest several directions for future research with regard to the contribution of 17βHSD1 to breast cancer progression and related treatment (Aka et al., 2012)

## 4. Inhibitor design

The search for inhibitors of 17β-HSDs began in the 1970s and gradually gained momentum thereafter before culminating during the first decade of the 2000s. Significantly more

inhibitors are known for the 17β-HSD1 than the other isoforms in the family. Several review articles reported structure–activity relationship studies, which are crucial for drug design and illustrate the huge diversity of 17β-HSD1 inhibitors (Brozic et al., 2008; Day et al., 2008, 2010;Marchais-Oberwinkler et al., 2011;Penning, 1996; Poirier, 2003, 2009, 2010, 2011). Despite many years of research, there are no inhibitors in clinical use to date. This very likely results from the fact that 17β-HSD1 has estrogens as substrates and products such as E2 that also exhibits high affinity towards the estrogen receptor alpha (Huang et al., 2001; Jin & Lin, 1999; Lin et al. 2013). Therefore, the design of inhibitors that are analogues of estrogens makes it difficult to eliminate residual estrogenic activity (Lin et al. 2013, Mazumdar et al. 2009).With the emergence of personalized medicine and diagnostic tests, the arrival of a potent 17β-HSD1 inhibitor in a clinical setting is highly anticipated to provide a new option for the treatment of women found to have a high expression of 17β-HSD1 and a low expression of aromatase in breast cancer tumor biopsies (Ayan et al., 2012; Maltais et al., 2011). Finally, the use of 17β-HSD1 inhibitors is also a promising approach for the treatment of other estrogen-dependent diseases, such as endometrial cancer (de Cremoux, 2011) and endometriosis (Saloniemi T, 2010), where the enzyme has been shown to be overexpressed (Maltais et al., 2014).

Studies have shown that steroidal inhibitors preferably bind in the SUB, exhibiting interactions stabilized by hydrophobic contacts and hydrogen bonds with Tyr155/Ser142 and His221/Glu282 residues lining the pocket, whereas non-steroidal inhibitors bind partially to the SUB, but primarily to COF (Negri et al. 2010). However, competitive NMR-experiments suggested that phytoestrogens interact neither with the SUB nor with the COF.. The dimer interface of 17β-HSD1 was proposed to be a possible binding site by docking studies (Michiels et al., 2009). Hybrid inhibitors interacting with both steroid and cofactor binding sites resulted in nanomolar binding affinity at the molecular level, based on the available 3D structure of 17β-HSD1 (Qiu et al, 2002; Poirier et al. 2003). Further improvement of the cell penetration is necessary.

#### 4.1.1. Non-steroidal compounds

Inhibitor I (Fig. 3) is a non-steroidal derivative with a pyrimidinone core, which was tested by Solvay Pharmaceuticals. In their animal model, human MCF-7 cells expressing 17β-HSD1 were inoculated in nude ovariectomized (OVX) mice and tumors generated in the presence of E1 (0.1 mol/kg/d) were treated for 28 days by subcutaneous (sc) injection with inhibitor I at a dose of 5 mol/kg/d (2.8 mg/kg/d). Since the estrogen-dependent MCF-7 breast cancer cells express different 17β-HSD isoforms (Laplante et al., 2009), the authors stably transfected the HEK293 cells with a plasmid expressing human 17β-HSD1. Compared to the non-treated controls (in the presence or absence of estrone), inhibitor I reduced tumor weight by 54% and tumor area by 75%. The same group also tested five steroidal inhibitors (estrone derivatives B10721325, B10720511, B10720512, B10720440 and B10715817) in the tumor xenograft model (understanding the effect of inhibitors on estrone-stimulated human cancer cell growth in nude mice) at a dose of 5 mol/kg/d (Husen et al.,2006). Compound B10720511 was more potent than the other analogues and reduced tumor weight by 86%. This compound also showed a dose-dependent effect in this xenograft study with an estimated $IC_{50}$ of 1.58 mol/kg/d (0.7 mg/kg/d). As an example, the

representative compound II (B10721325) reduced tumor weight by 60%. By measuring the uterine weight, the authors also observed that such compounds produced an antiestrogenic effect.

#### 4.1.2. Steroidal compounds

Sterix Ltd. used extensive structure-based drug design with available crystal structures of 17β-HSD1 and developed a family of steroidal inhibitors of 17β-HSD1 and selected compound III (STX1040) as a non-estrogenic candidate to be tested in a xenograft model (Day et al., 2008; Lawrence et al., 2005). The authors inoculated estrogen-dependent human T47D breast cancer cells into nude OVX mice to generate tumors that could be stimulated by E1. Although T47D cells express additional 17β-HSDs, such as types 7 and 12, it was demonstrated *in vitro* that 17β-HSD1 is responsible for transforming all E1 to E2 (Poirier et al., 2009, Laplante et al., 2009). Breast tumor growth in T47D cells was stimulated by E1 injection (0.05 or 0.1 μg E1/mouse/d) for 35 days. Subsequently after 35 days, animals that showed response to E1 dosing were provided with an additional dose of 20 mg/kg/day STX1040 daily for 28 days. STX1040 significantly inhibited E1 stimulated T47D cell proliferation and decreased tumor volumes. STX1040 also decreased the plasma concentration of E2 in the xenograft experiments and the authors determined that it did not work *via* ER antagonism (antiestrogen).

The last steroidal inhibitor of 17β-HSD1, compound IV (PBRM) has distinct mechanism of action, differing from the others. By replacing the phenolic -OH of E2 by a bromoethyl group and adding a characteristic carbamoyl benzyl side chain, the authors obtained a non-estrogenic compound that inhibited the enzyme (Maltais et al., 2011). This compound exhibited no binding to the ER, with no antiestrogenic function. The structure activity relationship study provided a new potent and steroidal nonestrogenic inhibitor of 17β-HSD1 named 3-{[(16β,17β)-3-(2-bromoethyl)-17-hydroxyestra-1(10),2,4-trien-16-yl]methyl}benzamide(23b). This compound specifically inhibited the transformation of E1 into E2 by 17β-HSD1 in T-47D cells ($IC_{50}$ = 83 nM) with no effect on 17β-HSD2, 17β-HSD7, 17β-HSD12, or CYP3A4 and did not stimulate the proliferation of estrogen-sensitive MCF-7 cells. Compound 23b is a competitive and irreversible inhibitor of 17β-HSD1 (Ayan et al.,2012; Maltais et al., 2014), compound IV (10 mg/kg/d, sc) completely blocked tumor growth stimulated by E1(0.1 g/mouse/d, sc) comparable to that of the control group level (without E1) (Lin et al.,2013). A compound 6-(3-hydroxyphenyl) naphthalene-2-ol (Compound 5 in Frotscher et al., 2008) was identified as a highly active inhibitor of 17β-HSD1 showing good selectivity towards 17β-HSD2, ERα and ERβ. Furthermore it displays a medium Caco-2 permeability, reasonable metabolic stability and low inhibition of the most important hepatic CYP enzymes. This compound will be used as a primary lead in subsequent drug design process (Frotscher et al., 2008).

Recently, it is reported that 6-hydroxybenzothiazole ketones as a new class of 17β-HSD1 inhibitors with a notable activity/selectivity profile (Miralinaghi et al., 2014). They modified the benzothiazole core by a systematic bioisosteric replacement for the purpose of further optimizing parameters. Thus, they identified a new 6-hydroxybenzothiophene derivative that displayed stronger inhibition of 17β-HSD1 ($IC_{50}$=13nM) with higher selectivity than a

benzothiazole analog. Another study focused on rational structural modifications to this compound class with the aim of gaining more insight into its structure-activity relationship (SAR). (4-Hydroxyphenyl)-(5-(3-hydroxyphenylsulfanyl)-thiophen-2-yl) methanone was discovered as a member of a novel potent class of human 17β-HSD1 inhibitors. Computational methods were used to elucidate its interactions with the target protein. The compound also showed activity towards the murine 17β-HSD1 enzyme and is thus a starting point for the design of compounds suitable for evaluation in an animal disease model (Abdelsamie et al., 2014).

## 5. Some disease-related mutations

Certain mutations in the 17β-HSD family are related to disease. 17β-HSD1 polymorphisms were investigated for 16 different indications, most of which deal with breast cancer (8 studies) (Sasano et al., 2008; Subramanian et al., 2008; Suzuki et al., 2007). Three of these eight breast cancer studies have some direct associations with 17β-HSD1 SNPs (Single-nucleotide polymorphism). In multiethnic women from the US (Feigelson et al., 2001) and in Malaysian women (Wu et al., 2003) the A-allele of the SNP rs605059 (A/G: Gly312Ser) was claimed to be of high-risk. However, this observation was not repeated by the same author (Feigelson et al., 2006). In one study the AA allele in SNP rs605059 correlated with higher serum estradiol concentrations in lean women (Setiawan et al., 2004), and in another study a 12 bp deletion in the 5′ flanking area of 17β-HSD1 was only shown to influence the recurrence rate of breast cancer (Kristensen et al., 2001). AG- and AA-alleles of SNP rs605059 (A/G: S312G) in 17β-HSD1 in Chinese women seem to relate to endometrial cancer, but there is no comparable situation in US women (Setiawan et al., 2004). Conversely, the A-allele has a higher risk of endometrosis in Japanese women.

Surprisingly, 17β-HSD1 polymorphisms might play a role in prostate cancer risk prediction. In a study with a large number of multiethnic men no overall association of haplotypes of four common SNPs in 17β-HSD1 (rs676387 (C/A), rs605059 (A/G), rs598126 (G/A), rs2010750 (C/T)) with prostate cancer were observed; however, two subgroups, Latinos and Japanese Americans, with the CAGC haplotype had a lower prostate cancer risk (Kraft et al., 2005). In non-Hispanic Caucasian men the minor allele of 17β-HSD1 SNP rs605059 (A/G) was more frequent among sporadic prostate cancer cases than among controls, but no statistically significant association could be detected (Cunningham et al., 2007). An Australian ovarian cancer study with patients and controls of Caucasian origin showed no association between ovarian cancer and 17β-HSD1 or 17β-HSD4 polymorphisms (Beesley et al., 2007). In addition to cancer, 17β-HSD1 polymorphisms were found to be related to other phenotypes including vasomotor symptoms (VMS) (Crandall et al., 2006), depression and some cognitive function in Chinese women (Kravitz et al., 2006). One study analyzed the association of three 17β-HSD1 SNPs, rs2830 (A/G), rs592389 (T/G), and rs615942 (G/T), with metabolic syndrome and diabetes in a group of multiethnic women (Lo et al., 2006). The likelihood of having diabetes among Caucasian women who are homozygous for the 17β-HSD1 polymorphisms is 4- to 7-fold greater compared with women who are heterozygous for these SNPs. On the other hand, the three 17β-HSD1 gene polymorphisms were not associated with metabolic syndrome in any racial/ethnic group (Lo et al., 2006).

## Acknowledgment

This work was supported by the operating grant from Canadian Institutes of Health Research (CIHR, MOP 97917) and the Major Key Basic Research Fundamental Program of Shanghai Science and Technology Committee, China (Grant NO.14JC1492300).

This review and the corresponding Gene Wiki article are written as part of the Gene Wiki Review series--a series resulting from collaboration between the journal GENE and the Gene Wiki Initiative. The Gene Wiki Initiative is supported by National Institutes of Health (GM089820). Additional support for Gene Wiki Reviews is provided by Elsevier, the publisher of GENE.

The corresponding Gene Wiki entry for this review can be found here: https://en.wikipedia.org/wiki/HSD17B1

## References

Abdelsamie AS, Bey E, Hanke N, Empting M, Hartmann RW, Frotscher M. Inhibition of 17β-HSD1: SAR of bicyclic substituted hydroxyphenylmethanones and discovery of new potent inhibitors with thioether linker. Eur J Med Chem 2014 7 23;82:394–406. doi: 10.1016/j.ejmech.2014.05.074. [PubMed: 24929290]

Aka JA, Mazumdar M, Chen CQ, Poirier D, Lin SX. 17beta-hydroxysteroid dehydrogenase type 1 stimulates breast cancer by dihydrotestosterone inactivation in addition to estradiol production. Mol Endocrinol 2010 4;24(4):832–45. doi: 10.1210/me.2009-0468. [PubMed: 20172961]

Aka JA, Mazumdar M, Lin SX. Reductive 17beta-hydroxysteroid dehydrogenases in the sulfatase pathway: critical in the cell proliferation of breast cancer. Mol Cell Endocrinol 2009 3 25;301(1–2): 183–90. doi: 10.1016/j.mce.2008.10.042. [PubMed: 19038308]

Aka JA, Zerradi M, Houle F, Huot J, Lin SX. 17beta-hydroxysteroid dehydrogenase type 1 modulates breast cancer protein profile and impacts cell migration. Breast Cancer Res 2012 6 12;14(3):R92. [PubMed: 22691413]

Alho-Richmond S, Lilienkampf A, Wähälä K. Active site analysis of 17beta-hydroxysteroid dehydrogenase type 1 enzyme complexes with SPROUT. Mol Cell Endocrinol 2006 3 27;248(1–2): 208–13. [PubMed: 16412556]

Ayan D, Maltais R, Roy J, Poirier D. A new nonestrogenic steroidal inhibitor of 17β-hydroxysteroid dehydrogenase type I blocks the estrogen-dependent breast cancer tumor growth induced by estrone. Mol Cancer Ther 2012 10;11(10):2096–104. doi: 10.1158/1535-7163.MCT-12-0299. [PubMed: 22914440]

Azzi A, Rehse PH, Zhu DW, Campbell RL, Labrie F, Lin SX. Crystal structure of human estrogenic 17β-hydroxysteroid dehydrogenase complexed with 17β-estradiol. Nat Struct Biol 1996; 3(8):665–668. DOI: 10.1038/nsb0896-665 [PubMed: 8756321]

Batzl C, Hausler A, Schieweck K et al. Pharmacology of nonsteroidal aromatase inhibitors. In: Pasqualini J, Katzenellenbogen B (eds): Hormone-dependent cancer 1996; Marcel Dekker, New York, 155–168.

Beesley J, Jordan SJ, Spurdle AB, Song H, Ramus SJ, Kjaer SK, Hogdall E, DiCioccio RA, McGuire V, Whittemore AS, Gayther SA, Pharoah PD, Webb PM, Chenevix-Trench G; Australian Ovarian Cancer Study Group; Australian Cancer Study (Ovarian Cancer); Australian Breast Cancer Family Study. Association between single-nucleotide polymorphisms in hormone metabolism and DNA repair genes and epithelial ovarian cancer: results from two Australian studies and an additional validation set. Cancer Epidemiol Biomarkers Prev 2007 12;16(12):2557–65. [PubMed: 18086758]

Bey E, Marchais-Oberwinkler S, Negri M, Kruchten P, Oster A, Klein T, Spadaro A, Werth R, Frotscher M, Birk B, Hartmann RW. New insights into the SAR and binding modes of bis(hydroxyphenyl)thiophenes and -benzenes: influence of additional substituents on 17beta-hydroxysteroid dehydrogenase type 1 (17beta-HSD1) inhibitory activity and selectivity. J Med Chem 2009 11 12;52(21):6724–43. doi: 10.1021/jm901195w. [PubMed: 19831396]

Breton R, Housset D, Mazza C, Fontecilla-Camps JC, The structure of a complex of human 17beta-hydroxysteroid dehydrogenase with estradiol and NADP+ identifies two principal targets for the design of inhibitors. Structure 1996; 4: 905–15. [PubMed: 8805577]

Brozic P, Lanisnik Risner T, Gobec S. Inhibitors of 17beta-hydroxysteroid dehydrogenase type 1. Curr Med Chem 2008;15(2):137–50. [PubMed: 18220769]

Buehner M, Ford GC, Moras D, Olsen KW, Rossman MG. D-glyceraldehyde-3-phosphate dehydrogenase: three-dimensional structure and evolutionary significance. Proc Natl Acad Sci U S A 1973 11;70(11):3052–4. [PubMed: 4361672]

Castoria G, Migliaccio A, Giovannelli P, Auricchio F. Cell proliferation regulated by estradiol receptor: Therapeutic implications. Steroids 2010 8-9; 75(8–9):524–7. doi: 10.1016/j.steroids.2009.10.007. [PubMed: 19879889]

Cicatiello L, Addeo R, Sasso A, Altucci L, Petrizzi VB, Borgo R, Cancemi M, Caporali S, Caristi S, Scafoglio C, Teti D, Bresciani F, Perillo B, Weisz A. Estrogens and progesterone promote persistent CCND1 gene activation during G1 by inducing transcriptional derepression via c-Jun/c-Fos/estrogen receptor (progesterone receptor) complex assembly to a distal regulatory element and recruitment of cyclin D1 to its own gene promoter. Mol Cell Biol 2004 8;24(16):7260–74. [PubMed: 15282324]

Crandall CJ, Crawford SL, Gold EB. Vasomotor symptom prevalence is associated with polymorphisms in sex steroid-metabolizing enzymes and receptors. Am J Med 2006 9;119(9 Suppl 1):S52–60. [PubMed: 16949389]

Cunningham JM, Hebbring SJ, McDonnell SK, Cicek MS, Christensen GB, Wang L, Jacobsen SJ, Cerhan JR, Blute ML, Schaid DJ, Thibodeau SN. Evaluation of genetic variations in the androgen and estrogen metabolic pathways as risk factors for sporadic and familial prostate cancer. Cancer Epidemiol Biomarkers Prev 2007 5;16(5):969–78. [PubMed: 17507624]

Day JM, Foster PA, Tutill HJ, Parsons MF, Newman SP, Chander SK, Allan GM, Lawrence HR, Vicker N, Potter BV, Reed MJ, Purohit A. 17beta-hydroxysteroid dehydrogenase Type 1, and not Type 12, is a target for endocrine therapy of hormone-dependent breast cancer. Int J Cancer 2008 5 1;122(9):1931–40. doi: 10.1002/ijc.23350. [PubMed: 18183589]

Day JM, Tutill HJ, Purohit A, Reed MJ. Design and validation of specific inhibitors of 17beta-hydroxysteroid dehydrogenases for therapeutic application in breast and prostate cancer, and in endometriosis. Endocr Relat Cancer 2008 9;15(3):665–92. doi: 10.1677/ERC-08-0042. [PubMed: 18541621]

de Cremoux P. Hormone therapy and breast cancer. Bull Cancer 2011 11;98(11):1311–9. doi: 10.1684/bdc.2011.1466. [PubMed: 22020743]

Feigelson HS, Cox DG, Cann HM, Wacholder S, Kaaks R, Henderson BE, Albanes D, Altshuler D, Berglund G, Berrino F, Bingham S, Buring JE, Burtt NP, Calle EE, Chanock SJ, Clavel-Chapelon F, Colditz G, Diver WR, Freedman ML, Haiman CA, Hankinson SE, Hayes RB, Hirschhorn JN, Hunter D, Kolonel LN, Kraft P, LeMarchand L, Linseisen J, Modi W, Navarro C, Peeters PH, Pike MC, Riboli E, Setiawan VW, Stram DO, Thomas G, Thun MJ, Tjonneland A, Trichopoulos D. Haplotype analysis of the HSD17B1 gene and risk of breast cancer: a comprehensive approach to multicenter analyses of prospective cohort studies. Cancer Res 2006 2 15;66(4):2468–75. [PubMed: 16489054]

Feigelson HS, McKean-Cowdin R, Coetzee GA, Stram DO, Kolonel LN, Henderson BE. Building a multigenic model of breast cancer susceptibility: CYP17 and HSD17B1 are two important candidates. Cancer Res 2001 1 15;61(2):785–9. [PubMed: 11212283]

Filling C, Berndt KD, Benach J, Knapp S, Prozorovski T, Nordling E, Ladenstein R, Jörnvall H, Oppermann U. Critical residues for structure and catalysis in short-chain dehydrogenases/reductases. J Biol Chem 2002 7 12;277(28):25677–84. [PubMed: 11976334]

Frotscher M, Ziegler E, Marchais-Oberwinkler S, Kruchten P, Neugebauer A, Fetzer L, Scherer C, Müller-Vieira U, Messinger J, Thole H, Hartmann RW. Design, synthesis, and biological evaluation of (hydroxyphenyl)naphthalene and -quinoline derivatives: potent and selective nonsteroidal inhibitors of 17beta-hydroxysteroid dehydrogenase type 1 (17beta-HSD1) for the treatment of estrogen-dependent diseases. J Med Chem 2008 4 10;51(7):2158–69. doi: 10.1021/jm701447v. [PubMed: 18324762]

Gangloff A, Shi R, Nahoum V, Lin SX. Pseudo-symmetry of C19 steroids, alternative binding orientations, and multispecificity in human estrogenic 17beta-hydroxysteroid dehydrogenase. FASEB J 2003 2;17(2):274–6. [PubMed: 12490543]

Ghosh D, Pletnev VZ, Zhu DW, Wawrzak Z, Duax WL, Pangborn W, Labrie F, Lin SX. Structure of human estrogenic 17 beta-hydroxysteroid dehydrogenase at 2.20 A resolution. Structure 1995a, 5 15;3(5):503–13. [PubMed: 7663947]

Ghosh D, Wawrzak Z, Pletnev VZ, Erman M, Duax WL, Pangborn W, Zhu DW, Labrie F, Lin SX. Molecular mechanism of inhibition of steroid dehydrogenases by licorice-derived steroid analogs in modulation of steroid receptor function. Ann. N. Y. Acad. Sci 1995b; 761:341–3 [PubMed: 7625731]

Ghosh D, Vihko P. Molecular mechanisms of estrogen recognition and 17-keto reduction by human 17beta-hydroxysteroid dehydrogenase 1. Chem Biol Interact 2001 1 30;130–132(1–3):637–50.

Hershberger PA, Vasquez AC, Kanterewicz B, Land S, Siegfried JM, Nichols M. Regulation of endogenous gene expression in human non-small cell lung cancer cells by estrogen receptor ligands. Cancer Res 2005 2 15;65(4):1598–605. [PubMed: 15735050]

Huang YW, Pineau I, Chang HJ, Azzi A, Bellemare V, Laberge S, Lin SX. Critical residues for the specificity of cofactors and substrates in human estrogenic 17beta-hydroxysteroid dehydrogenase 1: variants designed from the three-dimensional structure of the enzyme. Mol Endocrinol 2001 11;15(11):2010–20. [PubMed: 11682630]

Husen B, Huhtinen K, Poutanen M, Kangas L, Messinger J, Thole H. Evaluation of inhibitors for 17beta-hydroxysteroid dehydrogenase type 1 in vivo in immunodeficient mice inoculated with MCF-7 cells stably expressing the recombinant human enzyme. Mol Cell Endocrinol 2006 3 27;248(1–2):109–13. [PubMed: 16406284]

Hwang CC, Chang YH, Hsu CN, Hsu HH, Li CW, Pon HI. Mechanistic roles of Ser-114, Tyr-155, and Lys-159 in 3alpha-hydroxysteroid dehydrogenase/carbonyl reductase from Comamonas testosteroni. J Biol Chem 2005 2 4;280(5):3522–8. [PubMed: 15572373]

Jansson A. 17Beta-hydroxysteroid dehydrogenase enzymes and breast cancer. J Steroid Biochem Mol Biol 2009 3;114(1–2):64–7. doi: 10.1016/j.jsbmb.2008.12.012. [PubMed: 19167496]

Jin JZ, Lin SX. Human estrogenic 17beta-hydroxysteroid dehydrogenase: predominance of estrone reduction and its induction by NADPH. Biochem Biophys Res Commun 1999 6 7;259(2):489–93. [PubMed: 10362535]

Karavolas HJ, Baedecker ML, Engel LL. Human placental 17 beta-estradiol dehydrogenase. V. Purification and partial characterization of the diphosphopyridine nucleotide (triphosphopyridine nucleotide)-linked enzyme. J Biol Chem 1970 10 10;245(19):4948–52. [PubMed: 4394161]

Kraft P, Pharoah P, Chanock SJ, Albanes D, Kolonel LN, Hayes RB, Altshuler D, Andriole G, Berg C, Boeing H, Burtt NP, Bueno-de-Mesquita B, Calle EE, Cann H, Canzian F, Chen YC, Crawford DE, Dunning AM, Feigelson HS, Freedman ML, Gaziano JM, Giovannucci E, Gonzalez CA, Haiman CA, Hallmans G, Henderson BE, Hirschhorn JN, Hunter DJ, Kaaks R, Key T, Le Marchand L, Ma J, Overvad K, Palli D, Pike MC, Riboli E, Rodriguez C, Setiawan WV, Stampfer MJ, Stram DO, Thomas G, Thun MJ, Travis R, Trichopoulou A, Virtamo J, Wacholder S. Genetic variation in the HSD17B1 gene and risk of prostate cancer. PLoS Genet 2005 11;1(5):e68. [PubMed: 16311626]

Kravitz HM, Meyer PM, Seeman TE, Greendale GA, Sowers MR. Cognitive functioning and sex steroid hormone gene polymorphisms in women at midlife. Am J Med 2006 9;119(9 Suppl 1):S94–S102. [PubMed: 16949394]

Kristensen VN, Kure EH, Erikstein B, Harada N, Børresen-Dale A. Genetic susceptibility and environmental estrogen-like compounds. Mutat Res 2001 10 1;482(1–2):77–82. [PubMed: 11535251]

Labrie F, Luu-The V, Lin SX, Simard J, Labrie C, El-Alfy M, Pelletier G, Bélanger A. Intracrinology: role of the family of 17 beta-hydroxysteroid dehydrogenases in human physiology and disease. J Mol Endocrinol 2000 8;25(1):1–16. [PubMed: 10915214]

Laganière J, Deblois G, Lefebvre C, Bataille AR, Robert F, Giguère V. From the Cover: Location analysis of estrogen receptor alpha target promoters reveals that FOXA1 defines a domain of the estrogen response. Proc Natl Acad Sci U S A 2005 8 16;102(33):11651–6. [PubMed: 16087863]

Langer LJ, Engel LL. Human placental estradiol-17 beta dehydrogenase. I. Concentration, characterization and assay. J Biol Chem 1958 9;233(3):583–8. [PubMed: 13575417]

Laplante Y, Rancourt C, Poirier D. Relative involvement of three 17beta-hydroxysteroid dehydrogenases (types 1, 7 and 12) in the formation of estradiol in various breast cancer cell lines using selective inhibitors. Mol Cell Endocrinol 2009 3 25;301(1–2):146–53. doi: 10.1016/j.mce.2008.08.026. [PubMed: 18812208]

Lawrence HR, Vicker N, Allan GM, Smith A, Mahon MF, Tutill HJ, Purohit A, Reed MJ, Potter BV. Novel and potent 17beta-hydroxysteroid dehydrogenase type 1 inhibitors. J Med Chem 2005 4 21;48(8):2759–62. [PubMed: 15828812]

Li Y, Isomaa V, Pulkka A, Herva R, Peltoketo H, Vihko P. Expression of 3beta-hydroxysteroid dehydrogenase type 1, P450 aromatase, and 17beta-hydroxysteroid dehydrogenase types 1, 2, 5 and 7 mRNAs in human early and mid-gestation placentas. Placenta 2005 5;26(5):387–92. [PubMed: 15850643]

Li Y, Qin Li, Xiao ZJ, Wang YL, Herva R, Leng JH, Lang JH, Isomaa V, Piao YS, Expression of P450 aromatase and 17β-hydroxysteroid dehydrogenase type 1 at fetal-maternal interface during tubal pregnancy. J Steroid Biochem Mol Biol 2003; 87:241–246. doi:10.1016/j.jsbmb.2003.09.013. [PubMed: 14698204]

Lin SX, Han Q, Azzi A, Zhu DW, Gangloff A, Campbell RL. 3D-structure of human estrogenic 17beta-HSD1: binding with various steroids. J. Steroid Biochem. Mol. Biol 1999; 69: 425–429. [PubMed: 10419021]

Lin SX, Poirier D, Adamski J. A challenge for medicinal chemistry by the 17β-hydroxysteroid dehydrogenase superfamily: an integrated biological function and inhibition study. Curr Top Med Chem 2013;13(10):1164–71. [PubMed: 23647539]

Lin SX, Yang F, Jin JZ, Breton R, Zhu DW, Luu-The V, Labrie F. Subunit identity of the dimeric 17 beta-hydroxysteroid dehydrogenase from human placenta. J Biol Chem 1992 8 15;267(23):16182–7. [PubMed: 1322895]

Lin SX, Zhu DW, Azzi A, Campbell RL, Breton R, Labrie F, Ghosh D, Pletnev V, Duax WL, Pangborn W. Studies on the three-dimensional structure of estrogenic 17 beta-hydroxysteroid dehydrogenase. J Endocrinol 1996 9;150 Suppl:S13–20. [PubMed: 8943782]

Lo JC, Zhao X, Scuteri A, Brockwell S, Sowers MR. The association of genetic polymorphisms in sex hormone biosynthesis and action with insulin sensitivity and diabetes mellitus in women at midlife. Am J Med 2006 9;119(9 Suppl 1):S69–78.

Lukacik P, Kavanagh KL, Oppermann U. Structure and function of human 17beta-hydroxysteroid dehydrogenases. Mol Cell Endocrinol 2006 3 27;248(1–2):61–71. [PubMed: 16414178]

Luu-The V, Labrie C, Zhao HF, Couët J, Lachance Y, Simard J, Leblanc G, Côté J, Bérubé D, Gagné R, Labrie F. Characterization of cDNAs for human estradiol 17 beta-dehydrogenase and assignment of the gene to chromosome 17: evidence of two mRNA species with distinct 5'-termini in human placenta. Mol Endocrinol 1989 8;3(8):1301–9. [PubMed: 2779584]

MacIndoe JH. The hydrolysis of estrone sulfate and dehydroepiandrosterone sulfate by MCF-7 human breast cancer cells. Endocrinology 1988 9;123(3):1281–7. [PubMed: 2969800]

Mäentausta O, Sormunen R, Isomaa V, Lehto VP, Jouppila P, Vihko R. Immunohistochemical localization of 17 beta-hydroxysteroid dehydrogenase in the human endometrium during the menstrual cycle. Lab Invest 1991 11;65(5):582–7. [PubMed: 1721669]

Maltais R, Ayan D, Poirier D. Crucial Role of 3-Bromoethyl in Removing the Estrogenic Activity of 17β-HSD1 Inhibitor 16β-(m-Carbamoylbenzyl)estradiol. ACS Med Chem Lett 2011 9 8; 2(9): 678–681. doi: 10.1021/ml200093v. [PubMed: 21927646]

Maltais R, Ayan D, Trottier A, Barbeau X, Lagüe P, Bouchard JE, Poirier D. Discovery of a non-estrogenic irreversible inhibitor of 17β-hydroxysteroid dehydrogenase type 1 from 3-substituted-16β-(m-carbamoylbenzyl)-estradiol derivatives. J Med Chem 2014 1 9;57(1):204–22. doi: 10.1021/jm401639v. [PubMed: 24328103]

Marchais-Oberwinkler S, Henn C, Möller G, Klein T, Negri M, Oster A, Spadaro A, Werth R, Wetzel M, Xu K, Frotscher M, Mazumdar M, Fournier D, Zhu DW, Cadot C, Poirier D, Lin SX. Binary and ternary crystal structure analyses of a novel inhibitor of 17β-HSD type1: a lead compound for breast cancer therapy. Biochem J 2009; 424:357–66. [PubMed: 19929851]

Hartmann RW, Adamski J. 17β-Hydroxysteroid dehydrogenases (17β-HSDs) as therapeutic targets: protein structures, functions, and recent progress in inhibitor development. J Steroid Biochem Mol Biol 2011 5;125(1–2):66–82. doi: 10.1016/j.jsbmb.2010.12.013. [PubMed: 21193039]

Michiels PJ, Ludwig C, Stephan M, Fischer C, Möller G, Messinger J, van Dongen M, Thole H, Adamski J, Günther UL. Ligand-based NMR spectra demonstrate an additional phytoestrogen binding site for 17beta-hydroxysteroid dehydrogenase type 1. J Steroid Biochem Mol Biol 2009 11;117(4–5):93–8. doi: 10.1016/j.jsbmb.2009.07.004. [PubMed: 19631742]

Miralinaghi P, Schmitt C, Hartmann RW, Frotscher M, Engel M. 6-Hydroxybenzothiophene ketones: potent inhibitors of 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1) owing to favorable molecule geometry and conformational preorganization. ChemMedChem 2014 10;9(10):2294–308. doi: 10.1002/cmdc.201402050. [PubMed: 25044709]

Miyoshi Y, Ando A, Shiba E, Taguchi T, Tamaki Y, Noguchi S. Involvement of up-regulation of 17beta-hydroxysteroid dehydrogenase type 1 in maintenance of intratumoral high estradiol levels in postmenopausal breast cancers. Int J Cancer 2001 12 1;94(5):685–9. [PubMed: 11745463]

Negri M, Recanatini M, Hartmann RW. Insights in 17beta-HSD1 enzyme kinetics and ligand binding by dynamic motion investigation. PLoS One 2010 8 10;5(8):e12026. doi: 10.1371/journal.pone.0012026. [PubMed: 20706575]

Nguyen BL, Chetrite G, Pasqualini JR. Transformation of estrone and estradiol in hormone-dependent and hormone-independent human breast cancer cells. Effects of the antiestrogen ICI 164,384, danazol, and promegestone (R-5020). Breast Cancer Res Treat 1995 5;34(2):139–46. [PubMed: 7647331]

Pasqualini JR, Chetrite GS. Recent insight on the control of enzymes involved in estrogen formation and transformation in human breast cancer. J Steroid Biochem Mol Biol 2005 2; 93(2–5):221–36. [PubMed: 15860265]

Pasqualini JR, Chetrite G, Blacker C, Feinstein MC, Delalonde L, Talbi M, Maloche C. Concentrations of estrone, estradiol, and estrone sulfate and evaluation of sulfatase and aromatase activities in pre- and postmenopausal breast cancer patients. J Clin Endocrinol Metab 1996 4;81(4):1460–4. [PubMed: 8636351]

Pasqualini JR, Gelly C, Nguyen BL, Vella C. Importance of estrogen sulfates in breast cancer. J Steroid Biochem 1989;34(1–6):155–63. [PubMed: 2560511]

Pasqualini JR. The selective estrogen enzyme modulators in breast cancer: a review. Biochim Biophys Acta 2004 6 7;1654(2):123–43. [PubMed: 15172700]

Peltoketo H, Isomaa V, Mäentausta O, Vihko R. Complete amino acid sequence of human placental 17 beta-hydroxysteroid dehydrogenase deduced from cDNA. FEBS Lett 1988 10 24;239(1):73–7. [PubMed: 2846351]

Penning TM. 17β-hydroxysteroid dehydrogenase: inhibitors and inhibitors design. Endocr Relat Cancer 1996; 3:41–56. doi: 10.1677/erc.0.0030041.

Penning TM. Molecular endocrinology of hydroxysteroid dehydrogenases. Endocr Rev 1997 6;18(3): 281–305. [PubMed: 9183566]

Poirier D. 17beta-Hydroxysteroid dehydrogenase inhibitors: a patent review. Expert Opin Ther Pat 2010 9;20(9):1123–45. doi: 10.1517/13543776.2010.505604. [PubMed: 20645882]

Poirier D. Advances in development of inhibitors of 17beta hydroxysteroid dehydrogenases. Anticancer Agents Med Chem 2009 7;9(6):642–60. [PubMed: 19601747]

Poirier D. Contribution to the development of inhibitors of 17β-hydroxysteroid dehydrogenase types 1 and 7: key tools for studying and treating estrogen-dependent diseases. J Steroid Biochem Mol Biol 2011 5;125(1–2):83–94. doi: 10.1016/j.jsbmb.2010.12.007. [PubMed: 21182944]

Poirier D. Inhibitors of 17 beta-hydroxysteroid dehydrogenases. Curr Med Chem 2003 3;10(6):453–77. [PubMed: 12570693]

Poirier Boivin RP, Bérabé M, Lin SX. Synthesis of a First Estradiol-Adenosine Hybrid Compound. Synth. Commun 2003; 33:3183–3192

Poutanen M, Isomaa V, Peltoketo H, Vihko R. Role of 17 beta-hydroxysteroid dehydrogenase type 1 in endocrine and intracrine estradiol biosynthesis. J Steroid Biochem Mol Biol 1995 12;55(5–6):525–32. [PubMed: 8547177]

Puranen T, Poutanen M, Peltoketo H, Vihko P, Vihko RK. Site-directed mutagenesis of the putative active site of human 17β-hydroxysteroid dehydrogenase type 1. Biochem J 1994 11 15; 304(Pt 1): 289–293. [PubMed: 7998947]

Qiu W, Campbell RL, Gangloff A, Dupuis P, Boivin P, Tremblay MR, Poirier D, Lin SX. A concerted, rational design of 17beta-hydroxysteroid dehydrogenase inhibitors: complex structure with estradiol-adenosine hybrids with high affinity. FASEB J 2002 16:1829–31. [PubMed: 12223444]

Saloniemi T, Järvensivu P, Koskimies P, Jokela H, Lamminen T, Ghaem-Maghami S, Dina R, Damdimopoulou P, Mäkelä S, Perheentupa A, Kujari H, Brosens J, Poutanen M. Novel hydroxysteroid (17beta) dehydrogenase 1 inhibitors reverse estrogen-induced endometrial hyperplasia in transgenic mice. Am J Pathol 2010 3;176(3):1443–51. doi: 10.2353/ajpath.2010.090325. [PubMed: 20093485]

Santner SJ, Feil PD, Santen RJ. In situ estrogen production via the estrone sulfatase pathway in breast tumors: relative importance versus the aromatase pathway. J Clin Endocrinol Metab 1984 7;59(1): 29–33. [PubMed: 6725522]

Sasano H, Suzuki T, Miki Y, Moriya T. Intracrinology of estrogens and androgens in breast carcinoma. J Steroid Biochem Mol Biol 2008 2;108(3–5):181–5. [PubMed: 17933521]

Schwabe I, Husen B, Einspanier A. Expression of the estradiol-synthesizing 17beta-hydroxysteroid dehydrogenases type 1 and type 7 in the nonhuman primate Callithrix jacchus. Mol Cell Endocrinol 2001 1 22;171(1–2):187–92. [PubMed: 11165028]

Setiawan VW, Hankinson SE, Colditz GA, Hunter DJ, De Vivo I. HSD17B1 gene polymorphisms and risk of endometrial and breast cancer. Cancer Epidemiol Biomarkers Prev 2004 2;13(2):213–9. [PubMed: 14973105]

Sherbet DP, Papari-Zareei M, Khan N, Sharma KK, Brandmaier A, Rambally S, Chattopadhyay A, Andersson S, Agarwal AK, Auchus RJ. Cofactors, redox state, and directional preferences of hydroxysteroid dehydrogenases. Mol Cell Endocrinol 2007 2;265–266:83–8.

Shi R, Lin SX. Cofactor hydrogen bonding onto the protein main chain is conserved in the short-chain dehydrogenase/reductase family and contributes to nicotinamide orientation. J. Biol. Chem 2004; 271:16678–16685.

Subramanian A, Salhab M, Mokbel K. Oestrogen producing enzymes and mammary carcinogenesis: a review. Breast Cancer Res Treat 2008 9;111(2):191–202. [PubMed: 17934808]

Suzuki T, Miki Y, Moriya T, Akahira J, Hirakawa H, Ohuchi N, Sasano H. In situ production of sex steroids in human breast carcinoma. Med Mol Morphol 2007 9;40(3):121–7. [PubMed: 17874044]

Takeyama J, Suzuki T, Hirasawa G, Muramatsu Y, Nagura H, Iinuma K, Nakamura J, Kimura KI, Yoshihama M, Harada N, Andersson S, Sasano H. 17beta-hydroxysteroid dehydrogenase type 1 and 2 expression in the human fetus. J Clin Endocrinol Metab 2000 1;85(1):410–6. [PubMed: 10634418]

Verma MK, Miki Y, Abe K, Suzuki T, Niikawa H, Suzuki S, Kondo T, Sasano H. Intratumoral localization and activity of 17β-hydroxysteroid dehydrogenase type 1 in non-small cell lung cancer: a potent prognostic factor. J Transl Med 2013 7 9;11:167. doi: 10.1186/1479-5876-11-167. [PubMed: 23837683]

Verma MK, Miki Y, Sasano H. Sex steroid receptors in human lung diseases. J Steroid Biochem Mol Biol 2011 11;127(3–5):216–22. doi: 10.1016/j.jsbmb.2011.07.013. [PubMed: 21856418]

Wu AH, Seow A, Arakawa K, Van Den Berg D, Lee HP, Yu MC. HSD17B1 and CYP17 polymorphisms and breast cancer risk among Chinese women in Singapore. Int J Cancer 2003 4 20;104(4):450–7. [PubMed: 12584742]

Yang F, Zhu DW, Wang JY, Lin SX. Rapid purification yielding highly active 17beta-hydroxysteroid dehydrogenase: application of hydrophobic interaction and affinity fast protein liquid chromatography. J. Chromatogr 1992; 582:71–6. [PubMed: 1491061]

Zhang CY, Chen J, Yin DC, Lin SX. The Contribution of 17beta-Hydroxysteroid Dehydrogenase Type 1 to the Estradiol-Estrone Ratio in Estrogen-Sensitive Breast Cancer Cells. PLoS ONE 2012; 7 ( 1), e29835. doi: 10.1371/journal.pone.0029835. [PubMed: 22253796]

Zhang CY, Wang WQ, Chen J, Lin SX, 2014 Reductive 17beta-hydroxysteroid dehydrogenases which synthesize estradiol and inactivate dihydrotestosterone constitute major and concerted players in

ER+ breast cancer cells. J.Steroid. Biochem. Mole. Biol 150,24–34. doi: 10.1016/j.jsbmb.2014.09.017.

Zhu DW, Lee X, Breton R, Ghosh D, Pangborn W, Duax WL, Lin SX. Crystallization and preliminary X-ray diffraction analysis of the complex of human placental 17beta-hydroxysteroid dehydrogenase with NADP+. J. Mol. Biol 1993; 234:242–4. [PubMed: 8230203]

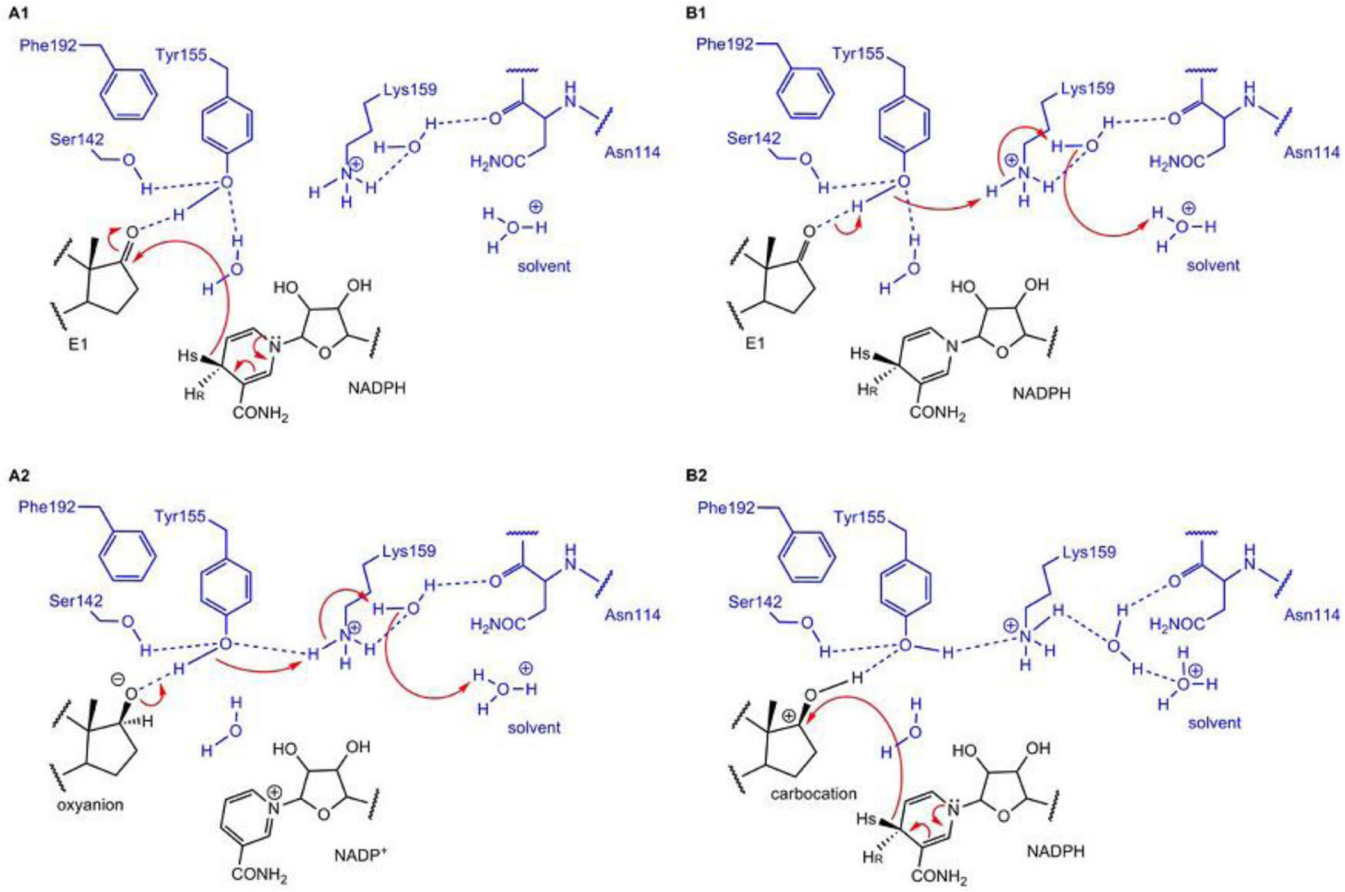


**Fig 1.**

Two possible stepwise catalytic mechanisms for 17β-HSD1. (A) In the first step the pro-S hydride of NADPH is transferred to the α-face of E1 at the planar C17 carbon (A1), resulting in an energetically favorable aromatic system; the resultant oxyanion is subsequently protonated by the acidic -OH group of Tyr155 (A2). (B) In the first step the keto oxygen of E1 is protonated by the acidic -OH of Tyr155 (B1); the resultant carbocation then accepts the pro-S hydride of NADPH at the α-face (B2). The proton relay is facilitated by a H-bond network involving Lys159, two water molecules and Asn114, an electrostatic interaction between the protonated side chain of Lys159 and the phenyl ring of Tyr155 (Ghosh & Vihko, 2001) as well as T-stacking between Phe192 and Tyr155 (Negri et al., 2010). Hydrogen bonds are represented by dashed lines. For the sake of clarity**π**–**π**-interactions are not depicted.

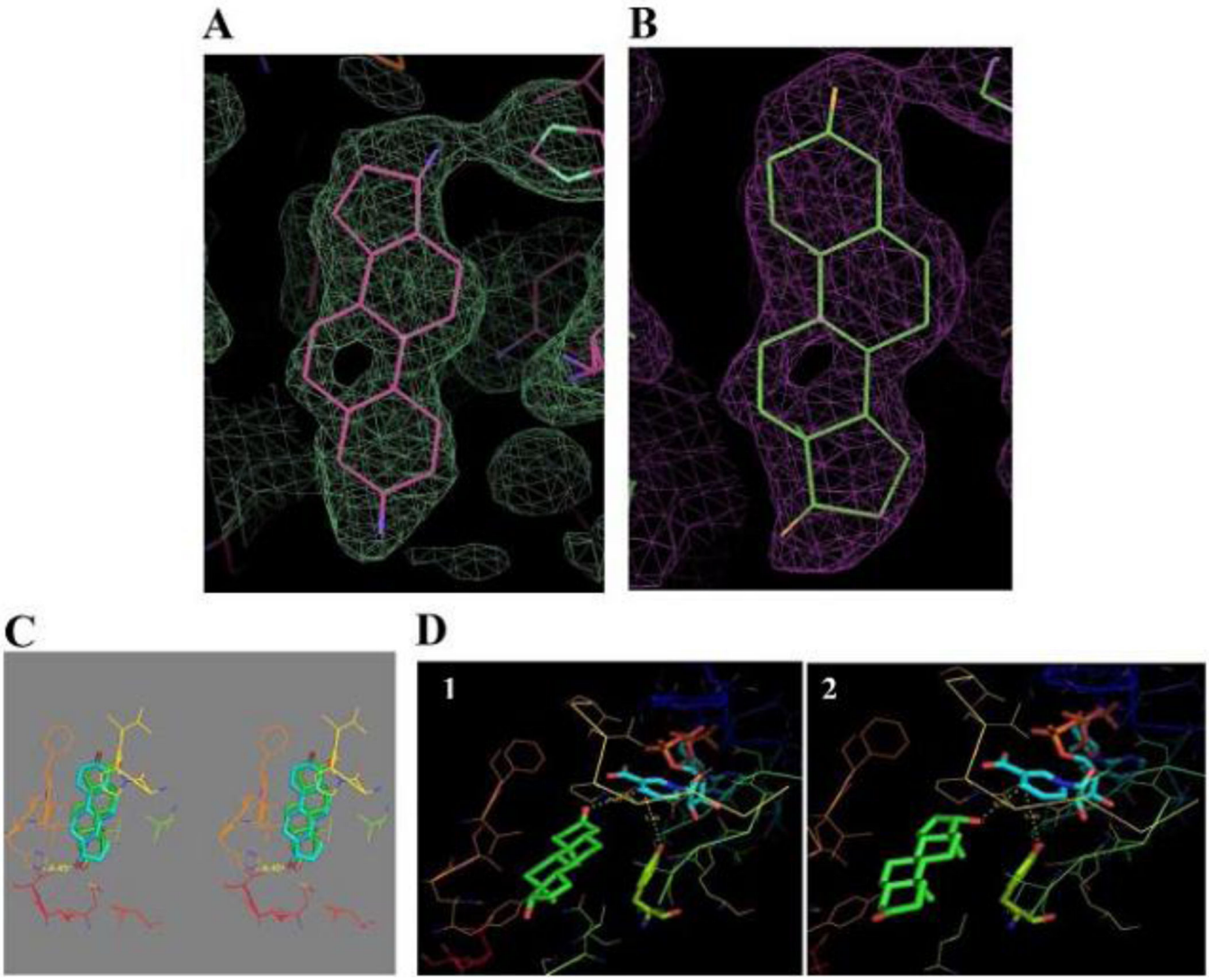


**FIG. 2.**

Crystal complex structure of 17β-HSD1/DHT. A and B, Electronic density of DHT for 2Fo-Fc map seen at 0.8σ cutoff in reverse binding mode (A) and normal binding mode (B). C, Stereo representation showing the H-bond of DHT with the residue His221 in the reverse binding mode (DHT represented in blue), whereas in the normal binding mode, there is no H-bond interaction present (DHT in green). D, Distances between DHT, Tyr155, and the cofactor NADP in 1) reverse mode (the distance between the O3 of DHT with NC4 of NADP is 4.35 Å and between Tyr155 to NC4 of NADP is 5.4 Å) and in 2) normal mode (the distance between the O17 of DHT with NC4 of NADP is 3.75 Å and between Tyr155 to NC4 of NADP is 5.4 Å). Note that the final model of the complex has been submitted to the protein data bank with PDB code 3KLM (Aka et al., 2010).

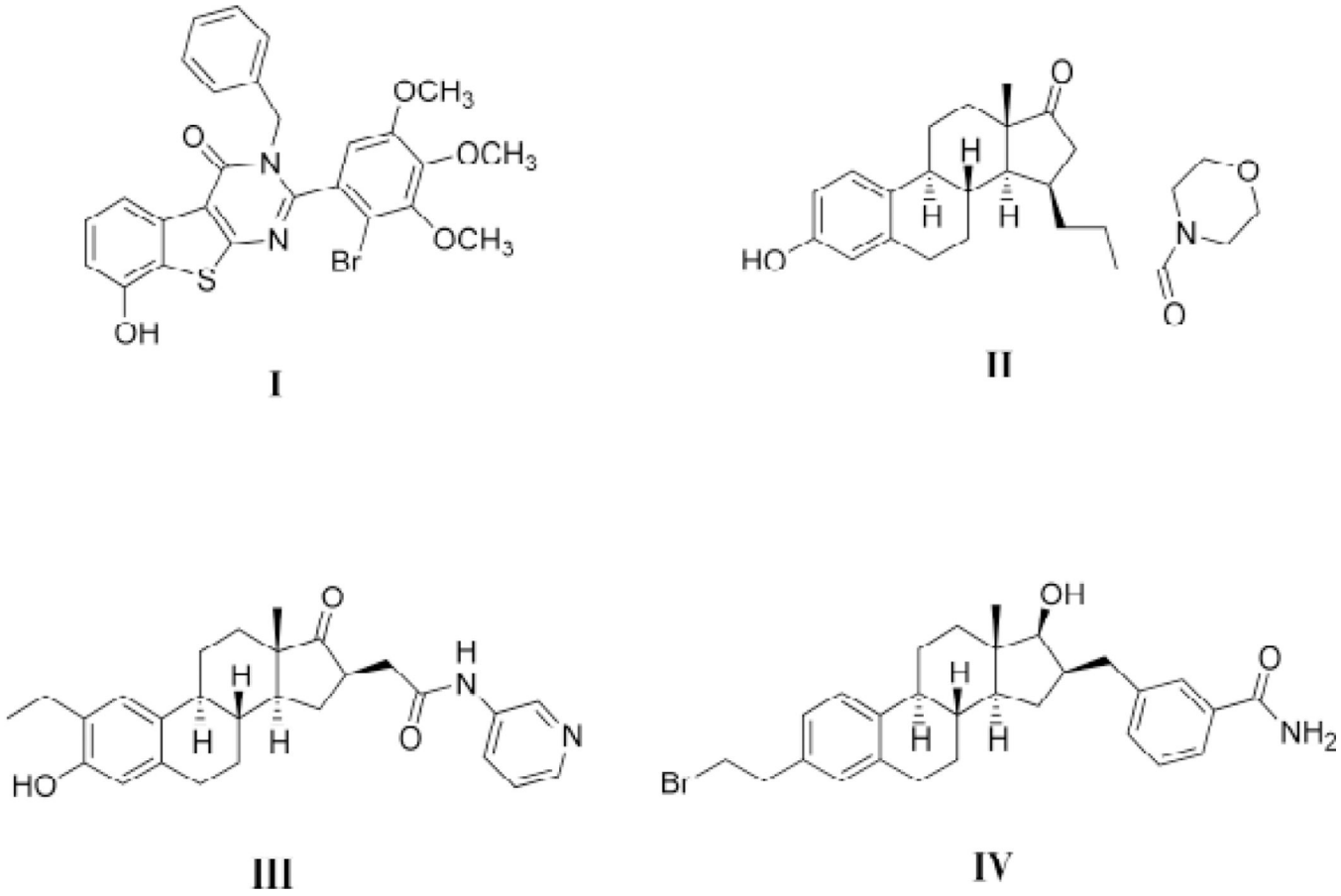


**Fig. (3).**

Representative inhibitors of 17β-HSD1, which demonstrated efficacy in reducing estrogen-dependent breast tumors *in vivo* (animal models). Cited from Lin et al., 2013.