Role of Hydroxysteroid (17beta) dehydrogenase type 1 in reproductive tissues and hormone-dependent diseases

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Short title: HSD17B1 in reproductive tissues and diseases

Abstract

Abnormal synthesis and metabolism of sex steroids is involved in the pathogenesis of various human diseases, such as endometriosis and cancers arising from the breast and uterus. Steroid biosynthesis is a multistep enzymatic process proceeding from cholesterol to highly active sex steroids via different intermediates. Human Hydroxysteroid (17beta) dehydrogenase 1 (HSD17B1) enzyme shows a high capacity to produce the highly active estrogen, estradiol, from a precursor hormone, estrone. However, the enzyme may also play a role in other steps of the steroid biosynthesis pathway. In this article, we have reviewed the literature on HSD17B1, and summarize the role of the enzyme in hormone-dependent diseases in women as evidenced by preclinical studies.

Identification of HSD17B1

Hydroxysteroid (17beta) dehydrogenase 1 (HSD17B1) is the first HSD17B enzyme identified, and is the one mostly studied of all the members of the family. Its structure and function have been extensively examined during the past decades (He et al. 2016). HSD17B1 protein was first isolated from human term placenta by Langer and Engel in 1958, and has been shown to be an enzyme efficiently catalyzing the conversion of a precursor estrogen estrone (E1) to the highly active estradiol (E2) (Langer and Engel 1958, Karavolas et al. 1970, Maentausta et al. 1990, Poutanen et al. 1993, Miettinen et al. 1996). *HSD17B1* cDNA was first identified in 1988 and was found to code for a protein consisting of 327 amino acids, with the predicted molecular weight of 34.8 kDa (Peltoketo et al. 1988, Gast et al. 1989, Luu The et al. 1989). The molecular weight reported for the purified, native HSD17B1 has varied from 33 kDa to 135 kDa in different studies and it has been suggested that the enzyme may exist as a monomer, dimer, trimer or even as a tetramer, and an equilibrium between these states has been proposed (Hagerman 1969, Engel and Groman 1974, Lin et al. 1992). Furthermore, in isoelectric focusing the enzyme migrates as five different forms (Engel and Groman 1974), suggesting that it undergoes post-translational modifications, which however, have not been further characterized. According to the current understanding and validated by crystallography, the predominant and active form of HSD17B1 is a non-covalently formed homodimer with two active sites (Engel and Groman 1974, Pons et al. 1977, Lin et al. 1992, Poutanen et al 1993, Ghosh et al. 1995, He et al. 2016, Hilborn et al. 2017).

Sequence analyses have shown that HSD17B enzymes appeared along with steroid receptors approximately 540 million years ago at the origin of vertebrates and functional Hsd17b1 enzyme has been characterized in early vertebrates, such as *Actinopterygii* (ray-finned fishes), including zebrafish. Furthermore, proteins sharing significant homology with human HSD17B1 have been identified, but not functionally characterized, in even earlier vertebrate classes, such as

Cephalochordata and *Echinodermata*, including amphioxus and sea urchins, respectively (Baker 2004, Mindnich and Adamski 2009, Albalat et al. 2011). Of the often-used preclinical models, rat *Hsd17b1* was identified from rat ovary in 1994 (Ghersevich et al. 1994a, Ghersevich et al. 1994b), followed by the cloning and characterization of mouse *Hsd17b1* in 1996 (Nokelainen et al. 1996). Analysis of the amino acid sequences showed that rat and mouse HSD17B1 sequences are 93 % identical to each other, 70 % and 68 % identical to human HSD17B1, respectively, whereas marmoset HSD17B1 shows 80 % identity to the human protein.

Enzymatic properties of human HSD17B1

Of the nicotineamide dinucleotide cofactors (NAD+/NADP+ and NADH/NADPH) utilized by the HSD17B enzymes, NAD+ is the most prevalent form in cells, followed by NADPH being approximately 10 times lower (Merker et al. 2002). Although HSD17B1 can bind to both NADP(H) and NAD(H), it is highly specific for NADPH, and the availability of NADPH is one of the key determinants of the reaction direction for HSD17B1 (Sherbet et al. 2009). The cellular NADPH concentration is 100-fold higher than that of NADP+, further favoring the catalysis of E1 to E2 by HSD17B1, and accordingly, in the cellular environment, the reaction is unidirectional and reductive (Poutanen et al. 1993, Gangloff et al. 2001). This was evidenced in studies where the expression of HSD17B1 was shown to decrease the oxidative E2 to E1 activity, while the reductive E1 to E2 activity was increased 23-fold (Poutanen et al. 1993, Miettinen et al. 1996, Puranen et al. 1997a, Day et al. 2008, Zhang et al. 2012). However, intracellular cofactor concentrations are affected by metabolism and respiration. For example, glucose deprivation lowering NADPH/NADP+-ratio was found to be a factor shifting the balance of HSD17B1 enzymatic reaction towards E2 oxidation (Sherbet et al. 2009). Furthermore, the cofactor availability in cancer cells can be different, and thus, may affect enzymatic reaction rates and directions (Moreira et al. 2016, Poljsak 2016).

In tissue homogenates and as a purified enzyme, human HSD17B1 mainly catalyzes the reduction of E1 to E2, and with a lower catalytic efficiency, the reverse reaction inactivating E2 to E1, as evidenced by various *in vitro* studies (Table 1). The K_m-values measured for E1 to E2 conversion by the human HSD17B1 vary between 0.36 to 1.38 μM, and 0.02 to 0.07 μM, in the presence of NADH and NADPH, respectively (Puranen et al. 1994, Puranen et al. 1997a, Jin and Lin 1999, Han et al. 2000, Gangloff et al. 2001). The K_m-values reported for the opposite reaction (E2 to E1) vary between 1.7 and 3.21 μM using NAD+, and the K_m was 4.16 μM with NADPH (Puranen et al. 1994, Puranen et al. 1997a, Puranen et al. 1997b, Jin and Lin 1999, Han et al. 2000).

In addition to HSD17B1, other HSD17Bs are also capable of converting E1 to E2 *in vitro*, including HSD17B2, HSD17B5 (also known as AKR1C3), HSD17B7 and HSD17B12, but the K_m-values reported for these enzymes are much higher than those reported for HSD17B1, as shown in Table 1. These enzymes also more efficiently catalyze other reactions, typically with non-steroidal substrates. The major substrates for HSD17B5 are the androgens androstenedione (A-dione) and dihydrotestosterone (DHT), as well as prostaglandin D2, but conversion of E1 to E2 with the K_m-value of 4 μM has been reported (Penning et al. 2000, Byrns et al. 2010). HSD17B7 catalyzes the conversion of E1 to E2 with a K_m-value of 3.25-4 μM, but its major role seems to be in cholesterol biosynthesis (Torn et al. 2003, Shehu et al. 2008, Jokela et al. 2010). HSD17B12 acts on prostaglandin synthesis and fatty acid elongation, but conversion of E1 to E2 has been reported with a K_m-value 3.05 μM (Luu-The et al. 2006). Despite the high K_m-values, HSD17B5, HSD17B7 and HSD17B12 have been shown to contribute to E2 production in breast cancer cells (Byrns et al. 2010, Zhang et al. 2015), suggesting biological significance for these enzymes also in estrogen production. Minor E2 production from E1 was also reported for HSD17B8 (Ohno et al. 2008), and yet additional enzymes might contribute to this reaction. For example, DHRS11 was recently reported to efficiently convert E1 to E2 in the presence of NADPH (K_m = 0.7 μM) (Endo et al. 2016). Although HSD17B1

expression in peripheral tissues is low, its catalytic efficacy to convert E1 to E2 is markedly higher compared to other known enzymes, as shown in Table 1, suggesting a central role for HSD17B1 in both ovarian and peripheral E2 formation in women. Activation of estrogens in physiological conditions by HSD17B1 has also been demonstrated in various preclinical models.

The substrate-binding site of HSD17B1 is highly complementary to the structure of estrogens, but pseudosymmetrical C19-steroids can also bind to it (Lin et al. 2006). However, there is a clear difference in the substrate specificity of human and rodent HSD17B1 enzymes. Unlike the human enzyme, the rodent HSD17B1 catalyzes the 17beta-reduction of androgens and estrogens with equal catalytic efficiency. The substrate specificity of HSD17B1 arises from a highly conserved region between amino acids 148-282 and the difference in the catalytic properties of human and rodent enzymes is mainly due to variations of amino acids 149, 152, 153 and 187 (Azzi et al. 1996, Puranen et al. 1997b, Han et al. 2000). Despite the strong preference of the human HSD17B1 for estrogens, it has also been shown to catalyze the conversion of A-dione to testosterone (T) in cell homogenates, cultured cells (Poutanen et al 1993, Puranen et al. 1997b) and *in vivo* (Saloniemi et al. 2007, Saloniemi et al. 2009). This activity was, however, clearly lower than the reduction of E1, being in line with the over 100-fold higher K_m for the conversion of A-dione to T compared to the conversion of E1 to E2 *in vitro* (Puranen et al. 1997b). Based on K_m-values, HSD17B3 and HSD17B5 are likely the major HSD17Bs converting A-dione to T (Moghrabi et al. 1998, McKeever et al. 2002, Sharma et al. 2006). HSD17B1 has also been shown to catalyze the conversion of T to A-dione *in vitro* with a K_m of 8.75 μM and applying NAD+ as a cofactor. In addition to HSD17B1, also HSD17B5, 6, 8, 10 and 14 have been shown to convert T to A-dione as shown in Table 1, but the K_m-value for HSD17B10 was not reported (He et al. 1999, Shafqat et al. 2003).

Interestingly, human HSD17B1 has also been shown to catalyze the inactivation of DHT to 3beta-androstanediol (K_m = 8 μM) and androstanedione (K_m = 11 μM) with NADH as a cofactor, and the production of delta5-androstenediol (A-diol) from dehydroepiandrostenedione (DHEA; K_m = 24 μM), by applying NADPH as a cofactor (Han et al. 2000, Gangloff et al. 2001, Gangloff et al. 2003). Even though the K_m-value for the DHT inactivation to 3beta-androstanediol is rather high, the potential role for this reaction in the regulation of breast cancer cell growth has been considered (Aka et al. 2010, Zhang et al. 2015). However, other HSD17Bs more efficiently catalyze these androgenic reactions. HSD17B5 and HSD17B7 have been shown to catalyze the oxidation of DHT to 3beta-androstanediol, with HSD17B7 having the lowest K_m-value of 2.6 μM. HSD17B5 also catalyzes the conversion of DHT to androstanedione with a K_m similar to that of HSD17B1 (K_m = 11 μM). The conversion of DHEA to A-diol, which can further be converted to T, has been reported for HSD17B3 and HSD17B5 (Moghrabi et al. 1998, Ferraldeschi et al. 2013).

To summarize, human HSD17B1 predominantly catalyzes the conversion of E1 to E2. Compared to other HSD17B enzymes, it has superior catalytic efficacy for the reaction, but it is also likely involved in the metabolism of different androgens. The predominant reaction directions and rates, however, are affected by the availability of the substrates, cofactors and other enzymes competing for the substrate availability. Excess of substrate also affects the kinetics of HSD17B1 (Gangloff et al. 2001, Han et al. 2017). Figure 1 further summarizes the role of HSD17B1 in androgen and estrogen biosynthesis.

Expression and regulation of HSD17B1

Genetic locus of HSD17B1

Human *HSD17B1* gene is located at chromosome 17, at the region q21.2 (Peltoketo et al. 1988, Luu The et al. 1989, Winqvist et al. 1990). Preceding the functional human *HSD17B1* gene, there is a

pseudogene *HSD17B1P*, which contains a premature stop codon and based on expression databases (UCSC, Fantom) is not transcribed. The duplication and the subsequent rapid inactivation of *HSD17B1P* are relatively recent evolutionary events, which occurred in *Hominoidae* and the pseudogene is not present in *Macacas* (Luu The et al. 1990, Peltoketo et al. 1992, Keller et al. 2006). According to current human genome assemblies, various transcripts are produced from the *HSD17B1* locus. Furthermore, two versions of the protein-coding transcript NM_000413.2 are produced: the shorter 1.3 kb form is the transcript that correlates with HSD17B1 protein and enzyme activity, whereas the longer 2.3 kb form is more broadly expressed and does not correlate equally well with protein and activity levels (Luu The et al. 1989, Tremblay et al. 1989, Luu-The et al. 1990, Poutanen et al. 1990, Poutanen et al. 1992a, Miettinen et al. 1996). The promoter of the 1.3 kb transcript encloses binding sites for various transcription factors, including AP2, CREB, ESR, GATA, SMAD, NGFIB, PGR, SF1, SP1, SP2 and SP3, of which CREB, ERE, NGFIB, GATA, SF1 and SP2 sites are conserved also in *Mus Musculus* (Peltoketo et al. 1992, Piao et al. 1995, Piao et al 1997a, Leivonen et al. 1999, Keller et al. 2006, Bak et al. 2009). Functional analyses *in vitro* have shown that mutating the SP1-binding site significantly reduced the promoter activity in choriocarcinoma cell lines, whereas GATA and AP2 site mutations resulted in increased activity and mutations to AP2 sites also reduced SP1 and SP3 binding (Piao et al. 1997a), suggesting that regulation by these factors is inter-related. Several research groups have also shown the presence of CpG islands inside the human and mouse genes and preceding the human *HSD17B1* right after the *HSD17B1P* gene (Luu The et al. 1989, Peltoketo et al. 1992, Rawluszko et al. 2011). According to analysis applying the UCSC genome browser, the CpG island in between *HSD17B1P* and *HSD17B1* is 695 bp long, whereas the length of the CpG island inside the human *HSD17B1* gene is 1807 bp. Compared to the relatively well-characterized 1.3 kb transcript promoter, the promoter for the 2.3 kb transcript is poorly studied. However, one study has reported it to be located in between the transposable *Alu* elements, which are

scattered throughout the genomic region containing the *HSD17B1P* and *HSD17B1* genes (Peltoketo et al. 1992).

HSD17B1 in steroid-synthesizing and target tissues

Human tissues with highest HSD17B1 expression are the ovaries and placenta, whereas in rodents, the high expression is restricted to the ovary only (Nokelainen et al. 1996, Mustonen et al. 1997, Moeller and Adamski 2009). The human ovaries and placenta synthesize large amounts of E2 to support ovarian folliculogenesis and to maintain pregnancy. The rodent placenta, on the contrary, does not produce estrogens and HSD17B1 is not expressed there (Nokelainen et al. 1996, Malassine et al. 2003). In the human ovaries, HSD17B1 is expressed in fetal and adult granulosa cells (Luu-The et al. 1990, Sawetawan et al. 1994, Vaskivuo et al. 2005), which, according to the two-step hypothesis of ovarian steroid production, are the site of estrogen production from the androgens synthesized by theca cells (McGee and Hsueh 2000, Miller and Auchus 2011). HSD17B1 expression in the ovary is related to the follicular differentiation stage and positively correlates with the follicular E2 concentration (Ghersevich et al. 1994c, Sawetawan et al. 1994, Vaskivuo et al. 2005). HSD17B1 is also expressed in the human corpus luteum, whereas luteinization in rodents induces a significant downregulation of the enzyme (Ghersevich et al. 1994a, Ghersevich et al. 1994c, Sawetawan et al. 1994). In the placenta, HSD17B1 is expressed in the syncytiotrophoblast cells involved in estrogen biosynthesis, and also in part of extravillous cytotrophoblast and in columnar cytotrophoblast cells, whereas there is no expression in villous trophoblasts (Fournet-Dulguerov et al. 1987, Miettinen et al. 1996, Li et al. 2003, Berkane et al. 2017). Lower levels of HSD17B1 expression have been reported in the classical steroid hormone target tissues the breast and endometrium (Maentausta et al. 1990, Maentausta et al. 1991a, Poutanen et al. 1992a, Miettinen et al. 1999, Colette et al. 2013). Although the ovary is the major tissue expressing HSD17B1 in mice, low amount of HSD17B1 has been detected in the adrenal glands, uterus, pituitary and sebaceous glands of the skin in female mice

(Nokelainen et al. 1996, Pelletier et al. 2004) and in tibial growth plate and metaphysis of the rat bone (van der Eerden et al. 2004), suggesting that peripheral steroid synthesis also occurs to some extent in mice similar to humans.

HSD17B1 in steroid-dependent diseases

HSD17B1 expression has been associated with many diseases of the classical steroid target tissues. In the endometrium and endometrial diseases, HSD17B1 is expressed at very low level. However, recent studies have provided evidence for the significance of HSD17B1 in endometrial diseases. These studies have shown that reductive HSD17B activity is increased in benign and malignant conditions originating from the endometrium. In endometriosis and leiomyomas, HSD17B1 expression and activity is increased compared to healthy endometrium and myometrium, respectively (Kasai et al. 2004, Dassen et al. 2007, Delvoux et al. 2009, Delvoux et al. 2014, Colette et al 2013). Similarly, increased HSD17B1 level in grade I endometrial cancer enhances the local estrogen production and stimulates tumor growth (Cornel et al. 2012, Konings et al. 2018). Furthermore, HSD17B1 expression predicts poor prognosis for endometrial cancer (Cornel et al. 2017). The potential role of HSD17B1 in the development and progression of breast cancer has been acknowledged for long time, while its detection has been challenging due to the low expression level in the majority of the breast tumors and endometrial disorders. However, various studies have reported HSD17B1 expression in breast cancer and HSD17B1 is considered important for the ESR-positive breast cancer progression. A significant portion (20-50 %) of primary breast cancers expresses HSD17B1 (Poutanen et al. 1992a, Gunnarsson et al. 2006, Jansson et al. 2009). Accordingly, studies with large cohorts of breast cancer patients have shown that low HSD17B2/HSD17B1-ratio is associated with high recurrence rate and HSD17B1 expression is associated with poor prognosis for tamoxifen therapy i.e. increased risk for relapse, shorter disease-free interval and worse survival (Gunnarsson et al. 2001, Gunnarsson et al. 2003, Oduwole et al.

2004, Gunnarsson et al. 2005, Gunnarsson et al. 2008). The role of HSD17B1 as a central mechanism for a tumor relapse is also supported by a study in which aromatase inhibitor neoadjuvant therapy was noted to lead to increment of HSD17B1 in postmenopausal estrogen receptor (ESR) 1-positive cancer, and was proposed to be a putative compensatory mechanism to maintain high levels of estrogen in the tumor tissue (Chanplakorn et al. 2010). Changes in HSD17B1 expression are also associated to other reproductive disorders. Increased HSD17B1 protein levels have been identified in the fallopian tube during tubal pregnancy (Li et al. 2003) and in cervical cancer (Tomaszewska et al. 2015), and reduced expression has been reported in preeclampsia, a life-threatening hypertensive disease where reduced estrogen level is one of the key pathogenic mechanisms (Ishibashi et al. 2012, Berkane et al. 2017). Interestingly, a reduced serum HSD17B1 concentration was shown to be an independent second trimester prognostic marker for preeclampsia (Ohkuchi et al. 2012).

HSD17B1 in other tissues and diseases

In addition to reproductive tissues strongly dependent on sex steroids, there is accumulating evidence that HSD17B1 is expressed in a variety of other tissues as well. These include e.g. adipose tissue (Bellemare et al. 2009, Campbell et al. 2013, Yamatani et al. 2013), skin (Hoppe et al. 2007, Inoue et al. 2011) and bone (Sasano et al. 1997). Furthermore, HSD17B1 expression has been reported, for instance, in both healthy and cancerous lung (Verma et al. 2013, Drzewiecka et al. 2015), stomach (Frycz et al. 2013), colon (Rawluszko et al. 2011), adrenals (Bassett et al. 2005), hippocampus (Beyenburg et al. 2000) and pituitary (Green et al. 1999). HSD17B1 expression was also shown to be higher in the lungs of patients with chronic obstructive pulmonary disease (Konings et al. 2017), as well as in the prefrontal cortex in late-stage Alzheimer's disease compared to healthy tissue and earlier disease stages (Luchetti et al. 2011). The increased HSD17B1 expression also associated with poor prognosis of lung cancer and gastric cancer and with lymph node metastasis in lung cancer (Verma et al. 2013, Drzewiecka et al. 2015, Chang et al. 2017). Summary of studies reporting

HSD17B1 expression is shown in Table 2. However, these studies should be critically evaluated, since there are possible biases for both RNA and protein detection of HSD17B1: The 2.3 kb RNA is known to be constitutively expressed and most studies reporting *HSD17B1* expression do not indicate whether they measured the 1.3 kb transcript only or also the 2.3 kb transcript. Therefore, validation at protein level is recommended. Also, when measuring enzymatic activity, it is important to keep in mind that there are other enzymes contributing to the enzymatic reactions, and thus, confirmation of the contribution of HSD17B1 enzyme to the reaction of interest by HSD17B1 inhibitor treatment is advisable.

Despite the above-described potential pitfalls, changes in HSD17B1 expression, however, are typically associated with poor prognosis in both classical hormone-dependent diseases and in diseases considered to be less dependent on steroid hormones. The role and effect of HSD17B1 in human diseases may also be modulated by the genetic haplotype as shown in Table 3. Especially the common polymorphism rs605059 (937 AA, AG, GG), which results in a serine to glycine amino acid substitution has been widely studied (Normand et al. 1993, Mannermaa et al. 1994, Puranen et al. 1994) and the different genotypes of this polymorphism have been associated with endometriosis, cervical tumors, longevity and amount of children, recurrent spontaneous abortions, overall cancer risk, breast cancer, hepatocellular carcinoma, Alzheimer's disease, colorectal cancer and serum E2 levels both in candidate gene studies and meta-analyses. Although high-powered genome-wide association studies are required to validate the presently reported associations, the candidate gene study-based association pattern resembles that of the expression pattern, suggesting that HSD17B1 plays a role in diseases of various tissue types. However, different groups have demonstrated that the rs605059 polymorphism does not affect the estrogenic activity and immunological properties of the enzyme (Puranen et al. 1994, Plourde et al. 2008).

Regulation of HSD17B1 expression

The regulation of *HSD17B1* expression in female reproductive tissues has been widely studied and the factors regulating the expression include sex steroids, peptide hormones, growth factors, cytokines, retinoic acids and micro RNAs (miRNAs). Table 4 summarizes studies on HSD17B1 regulation at RNA or protein level. Granulosa cells of developing follicles express HSD17B1 (Ghersevich et al. 1994c, Sawetawan et al. 1994), and various factors that enable the antral-to-preovulatory transition of follicles, including EGF, TGFA, FGF2 and IL1B (McGee and Hsueh 2000) also upregulate *HSD17B1* expression (Table 4). Similarly, many factors that stimulate breast cancer proliferation, including IL1 and TNFA, also upregulate *HSD17B1* expression in breast cancer cells (Nagasaki et al. 2009) (Table 4). Furthermore, various other cytokines and growth factors, such as IGF1 and 2, IL6 and IL1B, typically produced by inflammatory cells and adipocytes, have been shown to induce E1 to E2 activity in breast cancer cells (Adams et al. 1991, Singh and Reed 1991, Speirs et al. 1993, Duncan et al. 1994, Duncan and Reed 1995), suggesting that the inflammation process in breast tumors enhances the tumor-acquired estrogen biosynthesis ability. Furthermore, E1 to E2 activity was increased in breast fibroadenomas in the luteal phase compared to follicular phase and in patients using oral progestins (Fournier et al. 1982), suggesting a role for progestins in the regulation of *HSD17B1*, an action also shown in breast cancer cells *in vitro* (Poutanen et al. 1990). However, the regulation of *HSD17B1* beyond female reproductive tissues is still poorly understood. Recently, DNA methylation has been shown to regulate HSD17B1 expression in cell lines from lung-, colon- and gastric cancer (Rawluszko et al. 2011, Drzewiecka et al. 2015) and miRNA-based regulation was demonstrated in preeclampsia (Ishibashi et al. 2012).

In summary, human HSD17B1 is expressed in a wide variety of healthy and diseased tissues, where a change in HSD17B1 expression typically results in poor prognosis. Thus, HSD17B1 is considered as a promising drug target to treat hormone-dependent women's diseases. HSD17B1 inhibitor

molecules have been developed for a long time and some of them have also been tested in preclinical models as reviewed below.

The physiological role of HSD17B1 evidenced by knockout mice

Hsd17b1 knockout (HSD17B1KO) mice were recently generated by us using a construct available via the International Mouse Phenotyping Consortium. In the KO mice, the entire *Hsd17b1* gene was replaced by a *lacZ*-reporter gene that also demonstrated the high *Hsd17b1* gene expression in granulosa cells of the ovarian follicles. The data showed that HSD17B1 is not crucial for fetal, postnatal and pubertal development of mice (Hakkarainen et al. 2015). Also the uterus weight was normal, indicating normal circulating estrogen levels in HSD17B1KO females, while the enzymes involved in E2 synthesis in the absence of HSD17B1 remain to be characterized. However, as expected, lack of *Hsd17b1* resulted in increased ovarian E1/E2- and A-dione/T-ratios, as indicated by measuring the steroids by a high sensitivity GC-MS/MS (Nilsson et al. 2015). This was in line with the data indicating that HSD17B1 accounts for 75-95 % of the wild type mouse ovarian capacity to convert E1 to E2 *in vitro* (Hakkarainen et al. 2015). Interestingly, we observed a marked upregulation of *Cyp17a1* in the theca cells of the KO mice in all phases of the estrous cycle, an effect similar to that previously demonstrated in ESR-deficient mice (Couse et al. 2003). Thus, the lack of *Hsd17b1* in granulosa cells results in an inappropriate estrogen signaling between the granulosa and theca cells, resulting from the increased LH action and/or a paracrine mechanism for the action of E2 in the mouse ovary. We also concluded that the lack of *Hsd17b1* is directly or indirectly involved in the maintenance and function of corpora lutea, and accordingly, the expression of *Hsd17b7*, a marker for corpora lutea in mice, was dramatically reduced in HSD17B1KO ovaries compared to WT ovaries during pseudopregnancy. A balanced intraovarian concentration of steroids is vital for successful initiation and maintenance of pregnancy, and the results from HSD17B1KO mice demonstrated the important role for HSD17B1 in these processes.

To our surprise, our recent data indicate that HSD17B1 is also expressed in testicular Sertoli cells both in rodents and in primates (Hakkarainen et al. 2018). Especially, the high expression was identified in the Sertoli cells of fetal mouse testes, while the expression was reduced to undetectable level in postnatal testes. Sertoli cells have a central role in supporting the development of germ cells in the seminiferous tubules, and HSD17B1 seems to have an essential role in this process, as evidenced by the markedly reduced number of elongating spermatids in the KO males. Interestingly, we could not show alteration in the concentration of intratesticular or circulating androgens, while *Hsd17b3* expression was increased as a compensatory mechanism. Overall, the data obtained suggested that HSD17B1 activity during the fetal period is important for the proper maturation of Sertoli cells, and for their ability to maintain the cell-cell junctions and to support spermatogenesis in adult testes (Hakkarainen et al. 2018). Importantly, our results also show the expression of HSD17B1 in the Sertoli cells in primates as well as in humans, indicating the need to further study the potential role of HSD17B1 in the regulation of human spermatogenesis. Furthermore, human HSD17B1 expression has been shown in various other male tissues, including normal and cancerous prostate (Koh et al. 2002). A substantial amount of HSD17B1 RNA and protein have also been detected in human prostatic stromal and epithelial cell lines 6S and LAPC4, respectively, where the expression was positively regulated by TGFB (Liu et al. 2011). In the LnCap prostate cancer epithelial cell line, dutasteride treatment significantly upregulated *HSD17B1* mRNA expression (Biancolella et al. 2007).

Unexpectedly, in HSD17B1KO mice, the expression of the gene *Naglu* close to the 5' prime end of *Hsd17b1* gene was markedly suppressed in all tissues (Jokela et al. 2017). These two genes are separated by only a 0.7 kb-long DNA fragment. Based on the data obtained, we concluded that the physical disruption of the genomic region coding for *Hsd17b1* causes the downregulation of *Naglu*

due to the presence of a regulatory region within the *Hsd17b1* gene, or due to the altered chromatin structure induced by the reporter gene insertion. Interestingly, *Hsd17b1* and *Naglu* are not similarly expressed. While *Hsd17b1* is mainly expressed in the mouse gonads (Nokelainen et al. 1996, Pelletier et al. 2004), *Naglu* is broadly expressed both in gonadal and extragonadal tissues (Jokela et al. 2017). Downregulation of the *Naglu* gene is, however, also detected in tissues that do not express *Hsd17b1* and disrupting the *Naglu* gene does not affect *Hsd17b1* expression. The corresponding genomic regions in mouse and human differ in their structure, and in humans the sequence between *HSD17B1* and *NAGLU* is 8.6 kb in length, including the *HSD17B1P* pseudogene (Luu The et al. 1990, Peltoketo et al. 1992). Thus, a similar linkage between these neighboring genes might not exist in humans. However, it may be of interest to search for mutations affecting the *NAGLU* gene from the 3'-non-coding region.

We also demonstrated that the off-target effect, resulting in downregulation of *Naglu* gene is mainly responsible for the metabolic phenotype observed in the HSD17B1KO mice, including the markedly reduced fat mass typical for lysosomal diseases (Jokela et al. 2017). The metabolic phenotype was also identified in the preliminary screening of the KO mice by the International Mouse Phenotyping Consortium. Thus, the identified off-target phenotype speaks for the importance of careful phenotyping of the mouse models produced, in order to identify the mechanisms involved and to avoid wrong conclusions about the physiological role of a gene of interest.

Models for testing HSD17B1 inhibitors *in vivo*

As reviewed elsewhere in this issue, multiple drug candidates for inhibition of HSD17B1 have been developed, but thus far, the efficacies of only few of those have been tested *in vivo*. However, testing the efficacy and pharmacodynamics *in vivo* is a prerequisite when aiming at clinical applications, and this requires animal models with validated readouts of the target inhibition. In addition, HSD17B1

inhibitors with proven potency *in vivo* may serve as valuable investigational tools to obtain proof-of-concept level evidence for the HSD17B1-dependence of biological phenomena under study.

In general, it is acknowledged that compounds that are potent inhibitors of the human HSD17B1 enzyme are poor inhibitors of rodent HSD17B1 enzymes, despite the significant similarity in the amino acid sequences between the human and rodent enzymes (Mindnich and Adamski 2009, Moller et al. 2010). Consequently, preclinical models with human HSD17B1 expression are often applied (Table 5). HSD17B1-driven conversion of E1 to the biologically highly active E2 is the most exploited approach in the studies testing the efficacy of HSD17B1 inhibitors. Uterotrophic assays have been successfully applied in TG mice expressing both human *HSD17B1* and estrogen-response element connected to luciferase reporter gene (ERELuc) allowing both the tissue weight and the ERELuc reporter activity as readouts (Jarvensivu et al. 2015). Administration of E1 to these immature BiTG female mice increased their uterine weight and uterine tissue ERELuc reporter activity, which were attenuated by HSD17B1 inhibitors. Similar inhibitor responses on ERELuc reporter activity were measured from the livers of ovariectomized (OVX) adult BiTG mice (Jarvensivu et al. 2015). In addition to the uterotrophic and ERELuc reporter activity assays, xenograft tumors derived from HSD17B1-expressing estrogen-responsive human endometrial cancer cells or breast cancer cells have been applied. In the xenografts grown on chicken chorioallantoic membrane (CAM), topically administered HSD17B1 inhibitor reduced E1-induced endometrial cancer cell proliferation (Konings et al. 2018). In breast cancer xenograft tumors grown in athymic mice, HSD17B1-driven conversion of E1 to E2 was shown to trigger the formation and growth of HSD17B1-expressing tumors that was hindered by HSD17B1 inhibitors (Husen et al. 2006a, Husen et al. 2006b, Day et al. 2008, Ayan et al. 2012). Most of these studies (Husen et al. 2006a, Day et al. 2008, Ayan et al. 2012) applied OVX mice, in order to remove the ovarian contribution to E2 synthesis. Husen et al. 2006b, however, demonstrated that the tumor growth of HSD17B1-expressing MCF7 was similar in E1-supplemented

ovary-intact and OVX mice, and that HSD17B1 inhibitors dose-dependently reduced the tumor growth also in ovary-intact mice, suggesting minor impact of mouse ovarian HSD17B1 expression and hormones on tumor growth in this setting.

HSD17B1 inhibition has also been demonstrated in HSD17B1TG mice by measuring the conversion of intravenously administered [^{3}H]E1 to [^{3}H]E2 *in vivo* by measuring the relative concentrations of the [^{3}H]E1 and [^{3}H]E2 in blood and in a variety of peripheral target tissues, including the uterus and mammary gland (Lamminen et al. 2009, Saloniemi et al. 2010, Jarvensivu et al. 2018). When E1 was intravenously administered to the circulation, significant conversion to E2 was measured already 2 minutes after the E1 administration even in intact male and female mice, but more conversion was measured in MMTV-HSD17B1TG mice (Lamminen et al. 2009). In this model, an intraperitoneal administration of a HSD17B1 inhibitor prior to the E1 challenge reduced the E2 formation measured from blood (Lamminen et al. 2009). Until now, inhibitor responses on endogenous E2/E1-ratio in the uterus, mammary gland or other peripheral tissues of HSD17B1TG mice have not been reported. However, human HSD17B1 overexpression in these estrogen target tissues was shown to trigger the development of abnormalities, such as endometrial hyperplasia (Saloniemi et al. 2010) and mammary cancer (Jarvensivu et al. 2018) that are linked to increased local estrogen exposure. In the uterus of HSD17B1TG mice, HSD17B1 inhibitor treatment fully reversed the endometrial hyperplastic morphology of epithelial cells in the glandular compartment although it did not fully block the proliferation of luminal epithelial cells (Saloniemi et al. 2010). HSD17B1TG females developed mammary cancers at older age while mammary gland-restricted HSD17B1 expression induced mammary gland lesions and rupture of the myoepithelial cell layer accompanied with peri- and intraductal inflammation. Treatment of the mice bearing local HSD17B1-induced mammary gland lesions with an HSD17B1 inhibitor did not reverse the lesion phenotype although trends for reduced lesion number and epithelial cell proliferation were observed, whereas a treatment with an

antiestrogen ICI 182,780 fully abolished the mammary gland phenotype (Jarvensivu et al. 2018). These data demonstrate that HSD17B1 expression is causally linked to the development of estrogen-related diseases in the uterus and mammary gland, and that the conditions can to a great extent be alleviated or reversed by HSD17B1 inhibitors.

Besides the above described *in vivo* models with human HSD17B1 activity, HSD17B1 enzyme in primates presents with significant similarity to human HSD17B1, and many HSD17B1 inhibitors developed against the human enzyme are reported to inhibit the primate, especially marmoset, HSD17B1 enzyme (Moller et al. 2010, Henn et al. 2012, Trottier et al. 2017). Although the experimental use of marmoset models present with limited availability and high costs, they allow the monitoring of pain-related aspects that have clinical significance in some estrogen-related diseases, such as endometriosis. When marmoset monkeys with painful endometriosis lesions were orally administered with an HSD17B1 inhibitor, alleviation of pain-associated behavioral impairments was recorded (Arnold and Einspanier 2013). These studies demonstrate that the marmoset model offers a possibility to combine the target tissue responses with the pain relief response.

Challenges in testing HSD17B1 inhibitors *in vivo*

As described in Table 5, the estrogen-responsive, human HSD17B1-expressing xenografts in athymic OVX mice are commonly applied as models to test HSD17B1 inhibitor responses *in vivo*. In OVX mice, unlike in postmenopausal women, the peripheral estrogen production is minimal, and therefore, E1 supplementation to OVX mice is needed for sufficient tumor growth. Accordingly, assays based on HSD17B1-induced uterotrophic response or increased ERELuc reporter gene expression in immature and OVX animals require E1 supplementation. Selecting the E1 dose is of crucial importance as it should have negligible estrogenic effect on its own, but when converted to E2, it should clearly promote estrogen-mediated tumor or uterine growth. The physiological estrogen levels

in mice are 10-fold and 100-fold less than those of women for total estrogens and E1, respectively (Nilsson et al. 2015), and therefore, a relatively low E1 supplementation should be preferred to avoid adverse effects related to high estrogen dose in mice, such as skin rash, urine obstruction and bladder stone formation. However, MCF7- or T47D-based subcutaneous or orthotopic tumor growth in female mice require estrogen supplementation that is higher than that of the physiological level. As a result, only a very restricted window of E1 doses is applicable. Furthermore, each E1 administration method applied has its "pros" and "cons". Daily subcutaneous E1 injections are easy to perform but laborious, stressful to mice, and result in fluctuating estrogen concentrations. Subcutaneous E1-releasing pellets reduce the required animal handling, but the release of steroids is difficult to control and it has been shown that after the pellet implantation, the estrogen release rates are high and may take several weeks to stabilize (Theodorsson et al. 2005). Osmotic minipumps have more stable hormone release, but are expensive, large in size, may clog up especially when used to deliver poorly soluble compounds, such as HSD17B1 inhibitors, and need to be replaced at relatively short intervals being a relevant concern for long *in vivo* studies. Therefore, alternative hormone implants with stable low-dose release rates, such as polymer-based drug delivery systems, are of interest.

In the above-described xenograft studies using T47D or MCF7 cell lines, the HSD17B1 inhibitor treatments were started at very early phases of tumor development at the time when the tumors were very small (i.e. 1-5 weeks after the tumor cell injections). Even if the 4-5 week-long HSD17B1 inhibitor treatment resulted in smaller tumor masses compared to the non-treated mice in these set ups, the changes in tumor diameters were rather small, and thus, prone to measurement errors. Furthermore, the small difference in tumor size between the control and the inhibitor treatment restricts the possibility to determine dose-dependent effects of the inhibitors.

In female adult mice, HSD17B1 is mainly expressed in the ovaries. However, the conversion of E1 to E2 may not be specifically restricted to the ovaries and reproductive tissues, since E1 to E2 conversion is reported to occur in multiple mouse tissues such as the kidney, trachea, lungs, esophagus and adrenal glands (Milewich et al. 1985). In line with these early findings, high serum E2 concentrations were reported in athymic OVX female mice administered with different E1 doses (Colette et al. 2009). Similarly, we have found high serum E2 concentrations in ovariectomized athymic nu/nu mice bearing subcutaneous E1 pellets (Figure 2). These data indicate extragonadal conversion of E2 from supplemented E1 in female mice. Furthermore, HSD17B1 is likely not the only mouse enzyme converting E1 to E2. Mouse AKR1C6 and AKR1C18 enzymes, unlike their human counterparts, are reported to significantly convert E1 to E2 (Velica et al. 2009). In addition, human HSD17B5, HSD17B7, HSD17B12 and DHRS11 enzymes can produce E2 from E1 (Table 1) and may contribute to the E2 synthesis also in mice. The existence of peripheral enzymes other than HSD17B1 converting E1 to E2 is also supported by our recent studies that revealed a similar E1 to E2 conversion in mouse kidney tissue homogenates derived from wild type and HSD17B1KO mice (Jokela et al. 2017). Thus, the preclinical approaches aiming to test HSD17B1 inhibitor efficacy *in vivo* require careful optimization to avoid possible pitfalls described above and summarized in Figure 3 that would result in false negative findings caused by, for example, suboptimal E1 supplementation or the peripheral E1 to E2 conversion. However, further studies are required to increase understanding of the similarities and differences between mouse and human steroid metabolism.

Conclusions

In Figure 4 we summarize the role of HSD17B1 in both gonadal and extragonadal tissues. Human HSD17B1 metabolizes various estrogenic and androgenic substrates, but the conversion of E1 to E2 is highly preferred. It is widely expressed in women in various tissues synthesizing or targeted by steroids, but is also expressed in tissues considered to be less dependent on sex steroid action, and the

data from us and others suggest that HSD17B1 may also play a role in males. Mouse models are valuable tools to study the potential role of HSD17B1 in the development of diseases. However, it is important to be aware of the pitfalls of these models, such as the existence of other enzymes capable of E1 to E2 conversion in mice and the much lower serum estrogen concentrations in mice. Our studies in genetically modified mice have, however, provided physiological proof-of-concept evidence for 1) the importance of intracrine and paracrine modes of action of steroid signaling and 2) the HSD17B1-mediated induction of estrogen-dependent disease phenotypes. For example, the absence of HSD17B1 from granulosa cells induced a gene expression change in theca cells (Hakkarainen et al. 2015). Furthermore, local overexpression of human HSD17B1 in mouse mammary gland caused an estrogen-dependent inflammation-aided myoepithelial rupture and epithelial cell proliferation phenotype without the systemic estrogen level affected, as indicated by e.g. the unchanged uterus weight (Jarvensivu et al. 2018). Also the endometrial hyperplasia phenotype observed in transgenic mice overexpressing human HSD17B1, as well as the E1-induced increase in the uterus weight and epithelial cell proliferation, were efficiently reversed by treatments with HSD17B1 inhibitors (Saloniemi et al. 2010, Jarvensivu et al. 2015). These promising data from us and others support the applicability of HSD17B1 inhibitors to treat the known HSD17B1-driven estrogen-dependent diseases along with putative other yet unexplored indications.

Acknowledgements

We thank Professor Arthur Mayerhofer for allowing the use of the picture of human testis.

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Figure legends

Figure 1. Role of human HSD17B1 in androgen and estrogen biosynthesis. The HSD17B1 enzyme has been show to possess 17beta-reductive activity in various reactions of the androgen and estrogen biosynthesis pathway. Typically, the reactions are reversible *in vitro*, although the cofactor concentrations in cells and tissues strongly drive the reactions towards the reductive direction. HSD17B1 has also been shown to catalyze the 3beta-reduction of DHT to 3beta-androstanediol and the 17beta-oxidation of DHT to androstanedione. The reactions not involving HSD17B1 are shown as gray. The lowest K_m-value (μM) obtained *in vitro* is shown. *5α-diol = delta5-androstenediol, A-dione = androstenedione, 3β-diol = 3beta-androstanediol, CYP = cytochrome P450 family, DHEA = dihydroepiandrostenedione, E1 = estrone, E2 = estradiol, HSD3B = hydroxysteroid (3beta) dehydrogenase, HSD17B = hydroxysteroid (17beta) dehydrogenase, preg = pregnenolone, prog = progesterone, SRD5A = steroid (5alpha) reductase.*

Figure 2. Extragonadal conversion of E1 to E2 in mice. Serum E1 and E2 concentrations in ovariectomized athymic nu/nu female mice subcutaneously implanted with a commercial 0.05 mg/90d pellet releasing a calculated daily dose of 0.56 μg E1/d. Mice (7-8 weeks of age) were ovariectomized and subcutaneously implanted with E1 pellets (Innovative Research of America, USA) under isoflurane anesthesia. Forty-five days later, the mice were euthanized and blood was collected for serum by heart puncture. Serum steroid analyses were performed by using LC-MS/MS, which was also used to verify that the pellets contained only E1 and not E2 (Häkkinen et al. 2018). Unexpectedly, the serum E1 and E2 levels were close to each other after the E1 dosing. Similar results were obtained in two independent experiments (n = 3 per group in each experiment). These data

together with literature analysis suggest that E1 is peripherally converted to E2 in mice. *d = day, E1 = estrone, E2 = estradiol, HSD17B1 = hydroxysteroid (17beta) dehydrogenase 1.*

Figure 3. Preclinical *in vivo* models applied to test efficacy of HSD17B1 inhibitors with their benefits (PROS) and limitations (CONS). *E1 = estrone, E2 = estradiol, HSD17B1 = hydroxysteroid (17beta) dehydrogenase 1.*

Figure 4. Role of HSD17B1 in gonadal and extragonadal tissues. HSD17B1 plays a role in steroid synthesis in the gonads and extragonadal tissues, and is also expected to regulate the ligand availability in steroid-dependent diseases, including estrogen-dependent neoplasms. A) HSD17B1 is expressed in granulosa cells of cycling human and mouse ovaries, as shown by immunohistochemical staining on the left, where the human granulosa cell layer is indicated by G. The theca cell layer surrounding the granulosa cells is present between the granulosa cells ad the dashed line, indicated with T. The oocyte is indicated with O. In cycling ovaries, HSD17B1 and CYP19A1 are involved in the estradiol (E2) production from androgenic substrates synthesized by theca cells. B) In the testis, HSD17B1 is expressed in Sertoli cells (S), indicated by immunohistochemical staining of human testis on the left. Interestingly, deletion of Sertoli cell-expressed *Hsd17b1* in mice induces the upregulation of *Hsd17b3* in testicular Leydig cells despite the unchanged serum gonadotropin and sex steroid levels (Hakkarainen et al. 2018). C) HSD17B1 has been shown to be expressed in normal, premalignant and malignant mammary gland. In the normal mammary gland, HSD17B1 is primarily expressed in the epithelium where it produces E2. Upregulation of HSD17B1 in the mammary gland ductal epithelium in transgenic mice induces proliferation and inflammation, resulting in the development of precancerous lesions of the mammary gland (Jarvensivu et al. 2018), preceding breast cancer development. HSD17B1 is also expressed in a proportion of human breast cancers as shown by the immunohistochemical staining of human breast cancer of the left. *A-dione = androstenedione, T = testosterone, E1 = estrone, E2 = estradiol, HSD17B = hydroxysteroid (17beta) dehydrogenase.*

Figure 1.

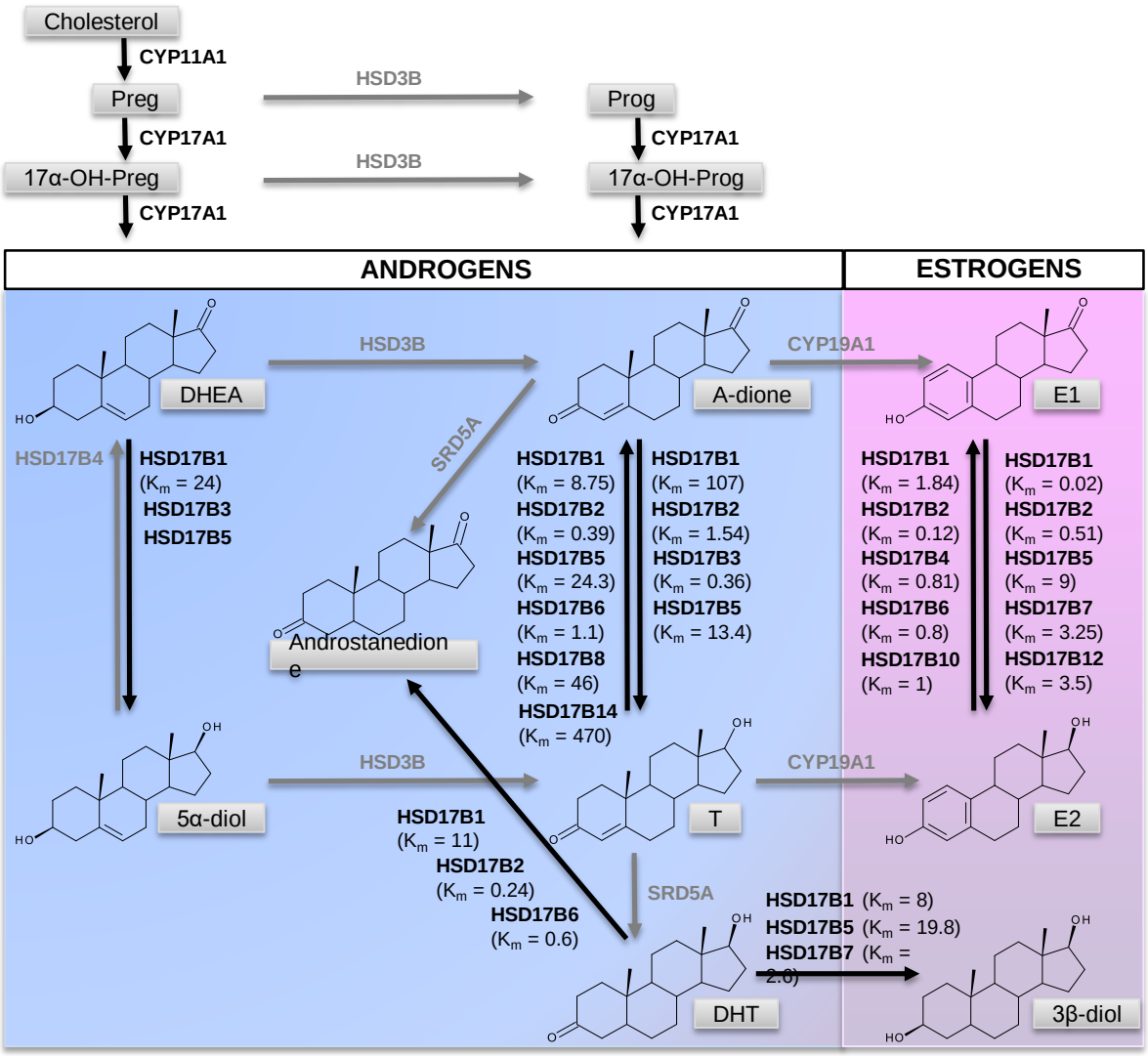

Figure 2.

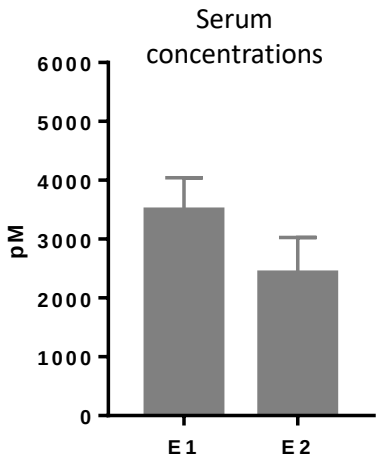

Figure 3

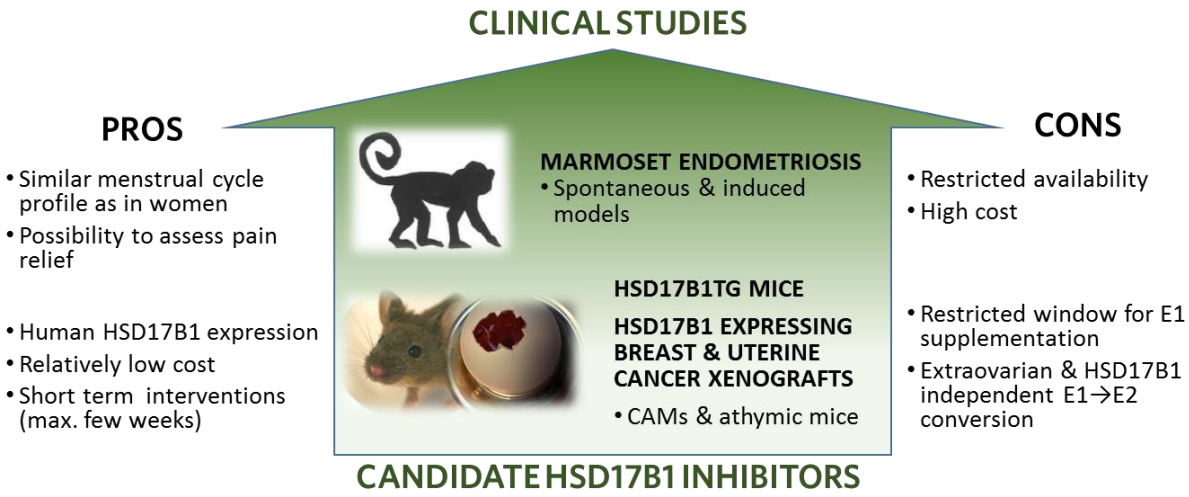

Figure 4.

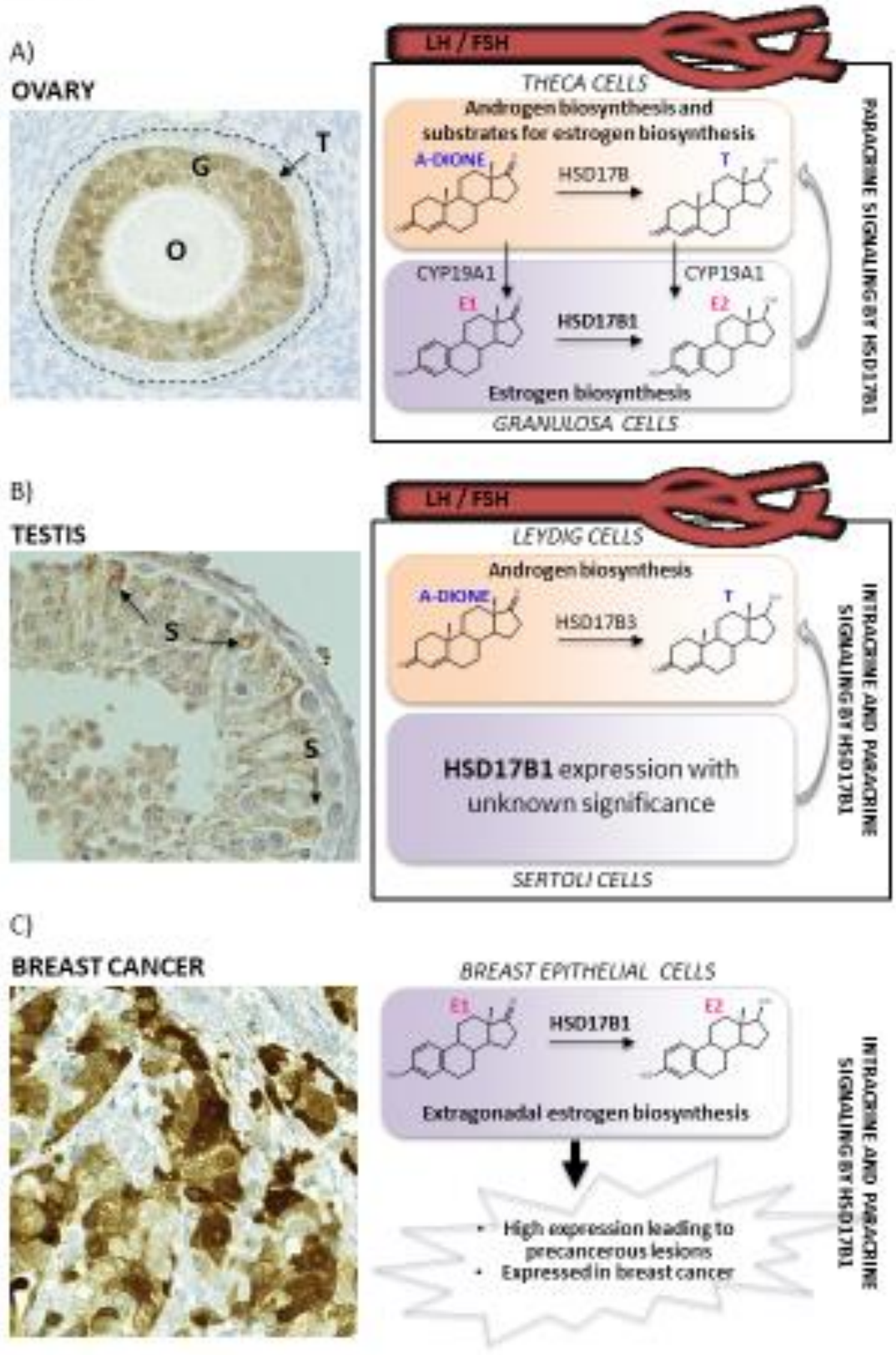

Table 1. Comparison of human HSD17Bs catalyzing same reactions with HSD17B1

HSD17B1 REACTION KINETICS				
Enzyme	**K_m-value (μM)**	**Study system**	**Cofactor**	**Reference**
ESTRONE TO ESTRADIOL CONVERSION (17beta reduction)				
HSD17B1	0.02	Cultured cells	NADPH	(Luu-The et al. 2006)
	0.42	Purified enzyme	NADH	(Gangloff et al. 2001)
	0.07	Purified enzyme	NADPH	(Gangloff et al. 2001)
	0.03	Purified enzyme	NADPH	(Han et al. 2000)
	0.36	Purified enzyme	NADH	(Jin and Lin 1999)
	0.03	Purified enzyme	NADPH	(Jin and Lin 1999)
	0.9	Purified enzyme	NADH	(Puranen et al. 1997a)
	1.38	Cell homogenate	NADH	(Puranen et al. 1997a)
	0.7	Cultured cells	NADH	(Puranen et al. 1997b)
	1.08	Cell culture supernatant	NADH	(Puranen et al. 1994)
HSD17B2	0.51	Purified enzyme	NADH	(Puranen et al. 1999)
	0.78	Cell homogenate	NADH	(Wu et al. 1993)
HSD17B5	9	Purified enzyme	NADPH	(Byrns et al. 2010)
HSD17B7	4	Cultured cells	NADPH	(Luu-The et al. 2006)
	3.25	Purified enzyme	NADPH	(Torn et al. 2003)
HSD17B12	3.5	Cultured cells	NADPH	(Luu-The et al. 2006)
ESTRADIOL TO ESTRONE CONVERSION (17beta oxidation)				
HSD17B1	4.6	Purified enzyme	NAD+	(Han et al. 2000)
	4.6	Purified enzyme	NADP+	(Jin and Lin 1999)
	1.7	Purified enzyme	NAD+	(Jin and Lin 1999)
	2.11	Purified enzyme	NAD+	(Puranen et al. 1997a)
	2.29	Cell homogenate	NAD+	(Puranen et al. 1997a)
	3.21	Cultured cells	NAD+	(Puranen et al. 1997b)
	1.84	Cell culture supernatant	NAD+	(Puranen et al. 1994)
HSD17B2	0.35	Purified enzyme	NAD+	(Puranen et al. 1999)
	0.12	Cell homogenate	NAD+	(Labrie et al. 1995)
	0.21	Cell homogenate	NAD+	(Wu et al. 1993)
HSD17B4	0.81	Cultured cells	NAD+	(Adamski et al. 1995)
HSD17B6	0.8	Cell lysate	NAD+	(Biswas and Russell 1997)
HSD17B8	118.5	Cell lysate	NAD+	(Ohno et al. 2008)
HSD17B10	43	Purified enzyme	NAD+	(Shafqat et al. 2003)
	11	Purified enzyme	NAD+	(He et al. 1999)

HSD17B14	5.6	Purified enzyme	NAD+	(Lukacik et al. 2007)
ANDROSTENEDIONE TO TESTOSTERONE CONVERSION (17beta reduction)				
HSD17B1	107.21	Cultured cells	NAD+	(Puranen et al. 1997b)
HSD17B2	1.54	Purified enzyme	NADH	(Puranen et al. 1999)
	2.63	Cell homogenate	NADH	(Wu et al. 1993)
HSD17B3	17.05	Cultured cells	NADPH	(McKeever et al. 2002)
	0.36	Cultured cells	NADPH	(Moghrabi et al. 1998)
HSD17B5	13.4	Purified enzyme	NADPH	(Sharma et al. 2006)
TESTOSTERONE TO ANDROSTENEDIONE CONVERSION (17beta oxidation)				
HSD17B1	8.75	Cultured cells	NAD+	(Puranen et al. 1997b)
HSD17B2	0.53	Purified enzyme	NAD+	(Puranen et al. 1999)
	0.4	Cell homogenate	NAD+	(Labrie et al. 1995)
	0.39	Cell homogenate	NAD+	(Wu et al. 1993)
HSD17B5	24.3	Purified enzyme	NAD+	(Penning et al. 2000)
HSD17B6	1.1	Cell lysate	NAD+	(Biswas and Russell 1997)
HSD17B8	46	Cell lysate	NAD+	(Ohno et al. 2008)
HSD17B14	470	Purified enzyme	NAD+	(Lukacik et al. 2007)
DIHYDROTESTOSTERONE TO 3BETA-ANDROSTANEDIOL CONVERSION (3beta reduction)				
HSD17B1	32	Purified enzyme	NADPH	(Gangloff et al. 2003)
	8	Purified enzyme	NADH	(Gangloff et al. 2003)
HSD17B5	19.8	Purified enzyme	NADH	(Penning et al. 2000)
HSD17B7	2.6	Purified enzyme	NADPH	(Torn et al. 2003)
DIHYDROTESTOSTERONE TO ANDROSTANEDIONE CONVERSION (17beta oxidation)				
HSD17B1	11	Purified enzyme	NAD+	(Gangloff et al. 2003)
	26	Purified enzyme	NADP+	(Gangloff et al. 2001)
	45	Purified enzyme	NADPH	(Han et al. 2000)
HSD17B2	0.24	Purified enzyme	NAD+	(Puranen et al. 1999)
	0.31	Cell homogenate	NAD+	(Wu et al. 1993)
HSD17B5	11.9	Purified enzyme	NADH	(Penning et al. 2000)
HSD17B6	0.5	Cell lysate	NAD+	(Biswas and Russell 1997)
DHEA TO ANDROSTENEDIOL CONVERSION (17beta reduction)				
HSD17B1	24	Purified enzyme	NADPH	(Gangloff et al. 2001)
	33	Purified enzyme	NADPH	(Han et al. 2000)

HSD17B = hydroxysteroid (17beta) dehydrogenase, NAD(H) = nicotineamide dinucleotide, NADP(H) = nicotineamide dinucleotide phosphate

Table 2. Human HSD17B1 expression

HSD17B1 EXPRESSION PROFILE IN HUMAN FEMALE TISSUES AND C			
HSD17B1 expression location	**RNA**	**Protein**	**Additional va**
	OVARY		
	Studies in tissues		
Ovarian surface epithelium and ovarian carcinoma tissue	Not studied	IHC	Not studied
Primary ovarian cancer and omentum tissues	qRT-PCR	Not studied	Not studied
Fetal-maternal interface of tubal pregnancy, fallopian tube in tubal pregnancy > fallopian tube during normal cycle	Not studied	IHC	Not studied
Ovarian corpus luteum tissue	ISH	Not studied	Not studied
Ovary	NB	Not studied	Not studied
Adult ovarian follicles, corpora lutea and cortex tissues	NB, sqRT-PCR	Not studied	Not studied
	Studies in cells		
Granulosa cell cultures	sqRT-PCR	Not studied	Not studied
Cultured and primary granulosa cells	NB	WB, IF, ELISA	E1 to E2 activ
	PLACENTA		
	Studies in tissues		
Healthy placental tissue > preeclamptic placenta	qRT-PCR	WB	Not studied
Chorion tissue before labor onset > at labor onset	qRT-PCR	Not studied	Not studied
Syncytiotrophoblast and extravillous cytotrobhoblast cells of placental tissue	ISH	IHC	Not studied
Syncytiotrophoblast cells of placental tissue	ISH	Not studied	Not studied
Placental tissue	NB	Not studied	Not studied
First trimester syncytiotrophoblast cells of placental tissue	Not studied	IHC, EM	Not studied
	Studies in cells		
JEG3 choriocarcinoma cell line	qRT-PCR	Not studied	Not studied
Primary trophoblast cells from term placenta tissue, JAR choriocarcinoma cells	qRT-PCR	WB	Not studied
JAR choriocarcinoma cells	qRT-PCR	Not studied	E1 to E2 activ
JEG3 choriocarcinoma cells	NB	WB	E1 to E2 activ
JEG, JAR, BeWO choriocarcinoma cell lines	NB	ELISA	E1 to E2 activ
Primary trophoblast cells from term placenta tissue, JEG and JAR choriocarcinoma cells	NB	Not studied	E1 to E2 activ
BEWO, JEG3 and JAR choriocarcinoma cell lines	NB	ELISA	E1 to E2 activ
BEWO, JEG3 and JAR choriocarcinoma cell lines	NB	ELISA	E1 to E2 activ
	FETAL		

Studies in tissues			
Human fetal liver tissue	qRT-PCR	Not studied	Not studied
Fetal granulosa cells of ovarian tissue (17^{th} week onwards)	ISH	Not studied	Not studied
11-21 week placenta, heart, brain, kidney, lung, adrenal gland, liver, gastrointestinal tract tissues	qRT-PCR	Not studied	E1 to E2 activ
Fetal ovary tissue	sqRT-PCR	Not studied	Not studied
UTERINE			
Studies in tissues			
Metastatic endometrial carcinoma > primary tumor tissues	qRT-PCR	Not studied	E1 to E2 activ and verified b HSD17B1 inh treatment
Endometrial cancer tissue	qRT-PCR	IHC	Not studied
Endometriosis > eutopic endometrium tissue	qRT-PCR	Not studied	E1 to E2 activ and confirmed HSD17B1 inh
Control and eutopic endometrium and endometriosis tissues	qRT-PCR	IHC	Not studied
ESR1-positive grade 1 endometrial carcinoma > healthy endometrium	qRT-PCR	IHC	E1 to E2 activ
Ovarian endometriosis > extraovarian endometriosis and endometrium tissues	qRT-PCR	Not studied	Not studied
Normal adjacent tissue > endometrial carcinoma	qRT-PCR	Not studied	Not studied
Mid-secretory endometrial tissue	qRT-PCR	IHC	Not studied
Normal proliferative endometrium > endometrium of PCOS patients	sqRT-PCR	Not studied	Not studied
Normal endometrium > endometrial cancer tissue	qRT-PCR	Not studied	Not studied
Ovarian endometriosis > normal endometrium tissue	qRT-PCR	Not studied	Not studied
Mid-secretory PCOS endometrium > normal endometrium	sqRT-PCR	Not studied	Not studied
Normal endometrium > endometriosis tissue	qRT-PCR	IHC	Not studied
Ovarian endometriosis > normal endometrium tissue	qRT-PCR	Not studied	Not studied
Normal endometrium > endometriosis lesion tissues	qRT-PCR	Not studied	Not studied
Leiomyoma > normal myometrium tissue	qRT-PCR, NB	Not studied	E1 to E2 activ
Myometrium tissue before labor onset > at labor onset	qRT-PCR	Not studied	Not studied
Endometrium and extraovarian endometriosis tissues	NB	Not studied	Not studied
Endometrium tissue	NB	ELISA (protein not detected)	Not studied
Untreated secretory endometrium > mifepristone-treated endometrium tissues	Not studied	IHC	Not studied
Endometrial adenocarcinoma tissue	Not studied	IHC	Not studied
Proliferative and secretory endometrium tissue	Not studied	IF	Not studied
Endometrial adenocarcinoma tissue	Not studied	ELISA	Not studied
Studies in cells			
Spheroid cultures of ovarian endometriosis > spheroid cultures of endometrium	qRT-PCR	IHC	E1 to E2 activ
Normal and endometrial cancer cell lines: HEC1A > Ishikawa > HIEEC	qRT-PCR	Not studied	E1 to E2 activ

Z12 endometriosis epithelial cell line	qRT-PCR	WB	
Human primary cervical fibroblasts	qRT-PCR	Not studied	Not studied
Endometrial primary stromal fibroblasts	qRT-PCR	Not studied	Not studied
ESR1-negative Ishikawa endometrial adenocarcinoma cell line	qRT-PCR	WB	
EM-1 endometrial glandular epithelial cell line	qRT-PCR	Not studied	Not studied
RL95-2 endometrial cell line	NB	ELISA	E1 to E2 activ
BREAST			
Studies in tissues			
Breast cancer tissue	Not studied	IHC	Not studied
ESR-positive, postmenopausal breast cancer tissue treated with aromatase inhibitor > breast cancer tissue before the treatment	Not studied	IHC	Not studied
ESR-positive and negative breast cancer tissue and normal adjacent tissue	qRT-PCR		No correlation and serum E2
Breast DCIS > benign breast disease tissue; postmenopausal benign breast disease > normal breast tissue	Not studied	IHC	Not studied
Postmenopausal breast cancer	Not studied	IHC	Not studied
Breast cancer and normal adjacent tissue	qRT-PCR	Not studied	Not studied
Postmenopausal, primary breast cancer tissue	qRT-PCR	Not studied	Not studied
Breast DCIS and IDC > normal breast tissue	qRT-PCR	IHC	Not studied
Postmenopausal, primary breast cancer tissue	Not studied	IHC	Not studied
Primary breast cancer tissue and soft tissue metastasis	qRT-PCR	Not studied	Not studied
Breast cancer tissue	qRT-PCR	Not studied	Not studied
Primary, postmenopausal breast cancer tissue	qRT-PCR	Not studied	Not studied
Breast cancer and normal premenopausal breast tissue	ISH	IHC	Not studied
Primary, postmenopausal breast cancer tissue	qRT-PCR	Not studied	Not studied
Recurrent > non-recurrent breast cancer tissue	qRT-PCR	Not studied	Not studied
Normal breast, breast DCIS, proliferative disease without atypia and atypical ductal hyperplasia	Not studied	IHC	Not studied
Breast IDC tissue	Not studied	IHC	Not studied
Epithelial cells of normal breast tissue	ISH	Not studied	
Normal breast tissue under hormonal contraception > throughout the menstrual cycle	Not studied	IHC	Negative corr serum E2 leve
Breast cancer tissue	NB	ELISA	
Invasive breast carcinoma tissue	Not studied	IHC	Not studied
Benign and malignant breast cancer tissue	Not studied	WB, IF	Not studied
Studies in cells			
MCF7 breast cancer cell line	sqRT-PCR	Not studied	Not studied
T47D breast cancer cell line	qRT-PCR	WB	E1 to E2 activ
Primary ESR-positive breast cancer cells	qRT-PCR	Not studied	mRNA correl ESR-activity
MCF7, HBL100 and BT474 breast cancer cell lines	qRT-PCR		
Breast cancer cell lines T47D, MCF7 and ZR751	Not studied	WB	Not studied
Breast and breast cancer cell lines MCF10A, HMEC, MCF7 and T47D	qRT-PCR	Not studied	Not studied
BT20 breast cancer cell line	NB	Not studied	E1 to E2 activ
HME4144, HME4224 human normal breast epithelial cells	NB	Not studied	E1 to E2 activ
T47D breast cancer cells	NB	WB	E1 to E2 activ

T47D, MDA-MB-361 breast cancer cell lines	NB	ELISA	E1 to E2 activ
T47D breast cancer cell line	NB	Not studied	E1 to E2 activ
BT20 , T47D, MDA-MB-361, ZR751	NB	ELISA, WB	Not studied
T47D breast cancer cell line	NB	ELISA	E1 to E2 activ
BLOOD CIRCULATION			
Studies in tissues			
Vena Cava tissue	Not studied	IHC	Not studied
Studies in plasma			
Plasma of healthy pregnant women > plasma of preeclamptic women	Not studied	ELISA	Not studied
Plasma during pregnancy > plasma throughout the menstrual cycle	Not studied	ELISA	Not studied
BONE			
Studies in tissues			
Bone tissue	Not studied	IHC	Not studied
Studies in cells			
Osteoblast-like cells and osteosarcoma cell lines HOS and MG63	sqRT-PCR	Not studied	Not studied
MG63 bone osteosarcoma cell line	qRT-PCR	Not studied	E1 to E2 activ
ADIPOSE			
Studies in tissues			
Adipose tissue from obese women > normal women	qRT-PCR	Not studied	Not studied
Subcutaneous adipose tissue before > after weight loss	Microarray		Correlation w level
Subcutanous abdominal and intra-abdominal adipose tissue	sqRT-PCR	Not studied	Not studied
Studies in cells			
Primary preadipocytes	qRT-PCR	WB (no protein detected)	
ADRENAL			
Studies in tissues			
Cortisol-producing adrenal adenoma tissue > normal adrenal tissue	Microarray	Not studied	Not studied
Studies in cells			
H295R adrenocortical cell line	qRT-PCR	Not studied	Not studied
THYROID			
Studies in tissues			
Thyroid tumor tissue	sqRT-PCR	Not studied	Not studied
LUNG			
Studies in tissues			
COPD lung > normal lung tissue	qRT-PCR	Not studied	Not studied
Non-small cell lung cancer tissue > normal lung	qRT-PCR	WB, IHC	Not studied
Non-small cell lung cancer tissue	Not studied	IHC	Protein level p correlated wit intratumoral E and negatively
Studies in cells			
A549 and CALU1 lung cancer cell lines	qRT-PCR	Not studied	E1 to E2 activ

LK87 and A549 lung cancer cell lines	qRT-PCR	WB	Not studied
CALU6, A549 and CALU1 lung cancer cell lines	qRT-PCR	WB	E1 to E2 activ
GASTROINTESTINAL SYSTEM			
Studies in tissues			
Gastric cancer and normal adjacent tissue	qRT-PCR	WB	Not studied
Normal adjacent tissue > colorectal cancer tissue	qRT-PCR	WB	Not studied
Studies in cells			
HGC27 and EPG85-275 gastric cancer cell lines	qRT-PCR	WB	E1 to E2 activ
HT29 colon cancer and SW707 colorectal carcinoma cell lines	qRT-PCR	WB	E1 to E2 activ
HT29 colon cancer and SW707 colorectal carcinoma cell lines	qRT-PCR	WB	E1 to E2 activ
BRAIN			
Studies in tissues			
Prefrontal cortex in late Alzheimer's disease > healthy and early stage disease tissues	qRT-PCR	Not studied	Not studied
Normal and diseased hippocampus tissues	sqRT-PCR	Not studied	Not studied
Normal pituitary and pituitary adenoma tissues	Not studied	IHC	Not studied
SKIN			
Studies in tissues			
Epidermis tissue	Not studied	IHC	Not studied
Studies in cells			
Purified human foreskin keratinocytes	NB, sqRT-PCR	Not studied	E1 to E2 activ
LYMPHOID			
Studies in cells			
Jurkat acute T-cell leukemia cells and HUT78 and RAJI B lymphoma cells	qRT-PCR	WB	E1 to E2 activ
HL60 cells and normal primitive myeloid progenitor cells	sqRT-PCR	Not studied	E1 to E2 activ
Peripheral blood mononucleocytes > Jurkat T-cell line > lymphoblastoid cell line B-LCL	sqRT-PCR	Not studied	Not studied
Lymphoblastoid cell line B-LCL, primary peripheral lymphocytes	sqRT-PCR	Not studied	Not studied
EYE			
Studies in tissues			
Lacrimal and meiobian gland tissues	qRT-PCR	Not studied	Not studied
Studies in cells			
Corneal and conjunctival cell lines	qRT-PCR	Not studied	Not studied

> = higher than, ELISA = Enzyme-linked immunosorbent assay, EM = electron microscopy, ESR = estrogen receptor, IF = immunofluorescense, IHC = immunohistochemistry, ISH = in situ hybridization, NB = Northern blotting, PCOS = polycystic ovary syndrome, qRT-PCR = quantitative real-time PCR, sqRT-PCR = semi-quantitative real-time PCR, WB = Western blotting, DCIS = ductal carcinoma in situ, IDC = invasive ductal carcinoma, COPD = chronic obstructive pulmonary disease

Table 3. HSD17B1 polymorphism association studies

ASSOCIATION OF HSD17B1 POLYMORPHISMS WITH CLINICAL FEMALE CONDITIONS

Polymorphism	Disease	Association	Reference
Rs605059 G allele	Infertility in stage I-II endometriosis patients	Yes	(Osinski et al. 2017)
Rs605059 AA allele	Increased risk of advanced stage cervical tumors	Yes	(Lutkowska et al. 2017)
Rs2676531, Rs2676530, rs676387	Amyloid polyneuropathy	No	(Santos et al. 2016)
Rs605059 GG allele	Reduced overall cancer risk in Caucasians (meta-analysis)	Yes	(Shi et al. 2016)
Rs605059	Risk of endometriosis	No	(Christofolini et al. 2015)
Rs605059	Serum estrogen level	No	(Hosono et al. 2015)
Rs605059	Endometrial cancer, leiomyoma, endometriosis (meta-analysis)	No	(Mu et al. 2015)
Rs605059 AA allele	Longevity in females	Yes	(Scarabino et al. 2015)
Rs605059 AA allele	High number of children	Yes	(Scarabino et al. 2015)
Rs605059 G allele	Recurrent spontaneous abortions	Yes	(Ntostis et al. 2015)
Rs676387 T allele	Increased hepatocellular carcinoma risk	Yes	(Zhang et al. 2014)
Rs605059 G allele	Protection from HRT-associated breast cancer	Yes	(Obazee et al. 2013)
Rs605059, rs676387	Advanced stage endometriosis	No	(Wu et al. 1993)
rs592389, rs676387, rs597255, rs2830	Gastric cancer risk	No	(Cho et al. 2012)
Rs605059 AA allele	Increased leiomyoma risk	Yes	(Cong et al. 2012)
Rs676387	Leiomymoma risk	No	(Cong et al. 2012)
Rs605059 AA allele	Increased endometriosis risk (meta-analysis)	Yes	(Hu et al. 2012)
Rs605059 GG allele, Rs676387 CC allele	Increased risk of Alzheimer's disease in Down syndrome female patients	Yes	(Lee et al. 2012)
Rs2830, Rs2676530, Rs598126	Alzheimer's disease risk	No	(Lee et al. 2012)
Rs605059	High myopia	No	(Chen et al. 2011)
Rs605059 A allele	Increased risk of endometriosis	Yes	(Lamp et al. 2011)
Rs605059 GG allele	Increased risk of colorectal cancer in women	Yes	(Sainz et al. 2011)
Rs2676530, rs676387	Endometriosis risk	No	(Trabert et al. 2011)
Rs605059 A allele	Increased breast cancer risk in postmenopausal hormonal therapy users	Yes	(MARIE-GENICA Consortium on Genetic Susceptibility for Menopausal Hormone

			Therapy Related Breast Cancer Risk 2010)
HSD17B1-7169del12	Breast cancer risk	No	(MARIE-GENICA Consortium on Genetic Susceptibility for Menopausal Hormone Therapy Related Breast Cancer Risk 2010)
Rs605059	Endometrial cancer	No	(Ashton et al. 2010)
Rs605059 A allele	Reduced breast cancer risk for women with high isoflavone intake	Yes	(Iwasaki et al. 2010)
Rs605059 GG allele	Reduced risk of breast cancer in Caucasians (meta-analysis)	Yes	(Yao et al. 2010)
Rs605059 GG allele	Increased breast cancer risk	Yes	(Kato et al. 2009)
Rs605059	Breast cancer risk	No	(Sangrajrang et al. 2009)
Rs605059, rs676387	Breast cancer risk (meta-analysis)	No	(Gaudet et al. 2008)
Rs676387 G allele	ER-positive breast cancer	Yes	(Hamaguchi et al. 2008)
Rs605059 GG allele	Reduced breast cancer risk in women with BMI <20	Yes	(Justenhoven et al. 2008)
Rs605059	Fibrocyctic breast tumor risk	No	(Sakoda et al. 2008)
Rs605059 A allele	Reduced risk of endometrial cancer	Yes	(Dai et al. 2007)
Rs605059 GG allele, rs598126 AA allele, rs2010750 AA allele	Increased ER-negative breast tumor risk	Yes	(Feigelson et al. 2006)
Rs676387 AA allele	Reduced ER-negative breast tumor risk	Yes	(Feigelson et al. 2006)
Rs605059	Breast cancer risk	No	(Silva et al. 2006)
Rs605059 A allele	Endometriosis risk	Yes	(Tsuchiya et al. 2005)
Rs605059	Serum sex steroid levels	No	(Dunning et al. 2004)
Rs605059, +1004C/T, +1322C/T	Risk of breast and endometrial cancer	No	(Setiawan et al. 2004)
Rs605059 AA allele, +1322 CA allele	Increased risk of breast cancer in obese postmenopausal women	Yes	(Setiawan et al. 2004)
Rs605059 AA allele	Higher E2 levels in lean women	Yes	(Setiawan et al. 2004)
-27 A<C	Risks of hormonal therapy	No	(Tempfer et al. 2004)
Rs605059	Serum E2 levels	No	(Travis et al. 2004)
Rs605059 AA allele	Increased risk of breast cancer enhanced by CYP17A1 polymorphisms	Yes	(Wu et al. 2003)
Rs605059 AA allele	Advanced breast cancer, but only in combination with CYP17A1 polymorphisms	Yes	(Feigelson et al. 2001)

Table 4. Regulation of HSD17B1 expression

SUMMARY OF STUDIES REPORTING HSD17B1 REGULATION				
Regulator	**Cell type**	**Organism**	**Effect**	**Reference**
Expression level in cultured cells				
STEROID HORMONES				
E2	Breast cancer cells	Human	↓	(Hilborn et al. 2017b)
E2	Lymphocytic cells	Human	↑	(Zhou and Speiser 1999)
Progestins	Endometriosis cells	Human	↓	(Mori et al. 2015)
Progestins	Endometriotic cells	Human	↓	(Beranic and Rizner 2012)
Progesterone	Breast cancer cells	Human	↑	(Poutanen et al. 1990, Poutanen et al. 1992a)
A-dione	Lymphocytic cells	Human	↑	(Zhou and Speiser 1999)
DHT	Breast cancer cells	Human	↓	(Hilborn et al. 2017b)
T + anastrozole	Breast cancer cells	Human	↑	(Gotte et al. 2009)
T	Lymphocytic cells	Human	↓	(Zhou and Speiser 1999)
E2	Granulosa cells	Rat	↑ with FSH only	(Ghersevich et al. 1994d)
DES	Granulosa cells	Rat	↑ with FSH only	(Ghersevich et al. 1994d)
DHT	Granulosa cells	Rat	↑ with FSH only	(Ghersevich et al. 1994d)
T	Granulosa cells	Rat	↑ with FSH only	(Ghersevich et al. 1994d)
PEPTIDE HORMONES AND CELL MESSENGERS				
8-Br-CAMP	Endometriosis cells	Human	↑	(Aghajanova et al. 2009)
8-Br-CAMP	Choriocarcinoma cells	Human	↑	(Piao et al. 1997b)
8-Br-CAMP	Choriocarcinoma cells	Human	↑	(Lewintre et al. 1994a)
8-Br-CAMP	Luteinized granulosa cells	Human	↓	(Tremblay et al. 1989)
8-Br-CAMP	Choriocarcinoma cells	Human	↑	(Tremblay et al. 1989)
8-Br-CAMP	Primary trophoblast cells	Human	↓	(Tremblay et al. 1989)
CRH	Primary trophoblast cells	Human	↑	(You et al. 2006)
Forskolin	Lymphoid cells	Human	↓	(Zhou and Speiser 1999)
8-Br-CAMP	Granulosa cells	Rat	↑	(Ghersevich et al. 2000)
8-Br-CAMP	Granulosa cells	Rat	↑	(Ghersevich et al. 1994d)
Follistatin	Granulosa cells	Rat	↓ with activin only	(Ghersevich et al. 2000)
Forskolin	Granulosa cells	Rat	↑	(Ghersevich et al. 1994d)
FSH	Granulosa cells	Rat	↑	(Ghersevich et al. 1994d)

FSH	Granulosa cells	Rat	↑	(Ghersevich et al. 2000)
FSH	Granulosa cells	Bovine	↑	(Zheng et al. 2008)
GROWTH FACTORS				
EGF	Choriocarcinoma cells	Human	↑	(Piao et al. 1997b)
EGF	Choriocarcinoma cells	Human	↑ via tyrosine kinase receptors	(Lewintre et al. 1994a)
FGF2	Choriocarcinoma cells	Human	↑	(Lewintre et al. 1994b)
TGFA	Choriocarcinoma cells	Human	↑ via tyrosine kinase receptors	(Lewintre et al. 1994a)
Activin	Gonadotroph cells	Mouse	↑ via Alk4 and Smad3	(Bak et al. 2009)
Activin	Granulosa cells	Mouse	↑ via Alk4	(Bak et al. 2009)
Activin	Granulosa cells	Rat	↑	(Ghersevich et al. 2000)
EFG	Granulosa cells	Rat	↓ with 8-Br-CAMP only	(Kaminski et al. 1997)
EGF	Granulosa cells	Rat	↓ with FSH only	(Ghersevich et al. 1994d)
EGF	Granulosa cells	Rat	↑	(Ghersevich et al. 1994d)
FGF2	Granulosa cells	Rat	↓ with 8-Br-CAMP only	(Kaminski et al. 1997)
TGFA	Granulosa cells	Rat	↓ with 8-Br-CAMP only	(Kaminski et al. 1997)
TGFB1	Granulosa cells	Rat	↑	(Kaminski et al. 1997)
TGFB1	Granulosa cells	Bovine	↑	(Zheng et al. 2009)
TGFB1	Granulosa cells	Bovine	↓ with FSH only	(Zheng et al. 2008)
CYTOKINES				
IL8	Breast epithelial cells	Human	↑	(Speirs et al. 1998)
IL8	Breast stromal cells	Human	↓	(Speirs et al. 1998)
TNFA	Glandular endometrial cells	Human	↑	(Salama et al. 2009)
IL1B	Granulosa cells	Rat	↓ with FSH, forskolin and 8-Br-CAMP only	(Ghersevich et al. 2001)
TNFA	Granulosa cells	Rat	↓ with FSH, forskolin and 8-Br-CAMP only	(Ghersevich et al. 2001)
RETINOIC ACIDS				
Retinoic acids	Choriocarcinoma cells	Human	↑	(Zhu et al. 2002)
Retinoic acids	Primary cytotrophoblast cells	Human	↑	(Zhu et al. 2002)
Retinoic acids	Choriocarcinoma cells	Human	↑	(Piao et al. 1997b)
Retinoic acids	Breast cancer cells	Human	↑	(Piao et al. 1997b)
MICRO-RNAs				
Mir17	Breast cancer cells	Human	↑	(Hilborn et al. 2017b)
Mir210	Breast cancer cells	Human	↑↓	(Hilborn et al. 2017b)
Mir7-5p	Breast cancer cells	Human	↑↓	(Hilborn et al. 2017b)

Mir1304-3p	Breast cancer cells	Human	↓	(Hilborn et al. 2017b)
Mir210	Choriocarcinoma cells	Human	↓	(Ishibashi et al. 2012)
Mir518	Choriocarcinoma cells	Human	↓	(Ishibashi et al. 2012)
CANCER-RELATED GENES				
CXCL1	Breast cancer cells	Human	↓	(Hilborn et al. 2017b)
EPHB6	Breast cancer cells	Human	↓	(Hilborn et al. 2017b)
KLK5	Breast cancer cells	Human	↓	(Hilborn et al. 2017b)
TP63	Breast cancer cells	Human	↓	(Hilborn et al. 2017b)
TRIM29	Breast cancer cells	Human	↓	(Hilborn et al. 2017b)
GREB1	Breast cancer cells	Human	↑	(Hilborn et al. 2017b)
HO1	Choriocarcinoma cells	Human	↑	(Tauber et al. 2010)
GENOME PACKING				
Methylation	Lung cancer cell lines	Human	↓	(Drzewiecka et al. 2015)
Methylation	Gastric cancer cell lines	Human	↓	(Drzewiecka et al. 2015)
Methylation	Colorectal cancer cells	Human	↓	(Rawluszko et al. 2011a)
Apidicin (HDAC inhibitor)	Endometrial cancer cells	Human	↓	(Keles et al. 2011)
OTHER FACTORS				
AFB1	Choriocarcinoma cells	Human	↑	(Huuskonen et al. 2013)
BPA	Endometrial cells	Human	↓	(Aghajanova and Giudice 2011)
Butyrate	Colorectal cancer cells	Human	↑	(Rawluszko et al. 2011b)
Calcium ionophore	Choriocarcinoma cells	Human	↑	(Piao et al. 1997b)
DHA	Primary cytotrophoblasts, JAT choriocarcinoma cells	Human	↑ □LUT□ and AP1-□□□□□□□□	(Wang et al. 2014)
Letrozole	Lung cancer cells	Human	↑	(Verma et al. 2013)
1,25-$(OH)_2D_3$	Purified foreskin keratinocyte cells	Human	↑	(Hughes et al. 1997)
Organotin compounds	Choriocarcinoma cells	Human	↑	(Nakanishi et al. 2006)
PMA	Choriocarcinoma cells	Human	↑	(Piao et al. 1997b)
PMA	Choriocarcinoma cells	Human	↑ with CAMP only	(Tremblay et al. 1989)
MXC	Antral follicle cultures	Mouse	↓	(Basavarajappa et al. 2011)
PMA	Granulosa cells	Rat	↑ with CAMP only	(Kaminski et al. 1997)
TCDD	Antral follicle cultures	Mouse	↓	(Karman et al. 2012)
VPA	Granulosa cells	Bovine	↓ with FSH only	(Glister et al. 2012)
Expression at whole organism level				
Progesterone	Endometrium tissue	Human	↑	(Maentausta et al. 1991a)
Progesterone	Endometrial carcinoma tissue	Human	↓	(Maentausta et al. 1992)

E1	Endometrial carcinoma tissue	Human	↓	(Maentausta et al. 1992)
Antiprogestin	Endometrium tissue	Human	↓	(Maentausta et al. 1993)
PMSG	Granulosa cells	Rat	↑	(Ghersevich et al. 1994b)
hCG	Granulosa cells	Rat	↓	(Ghersevich et al. 1994b)
FSH	Granulosa cells	Rat	↑	(Ghersevich et al. 1994a)
DES	Granulosa cells	Rat	↑	(Ghersevich et al. 1994a)
DES + FSH	Granulosa cells	Rat	↓	(Ghersevich et al. 1994a)
DBP	Whole ovary	Mouse	↑	(Sen et al. 2015)
DEN	Liver tissue	Mouse	↑	(Lee et al. 2017)

AFB1 = alphatoxin B1, A-dione = androstenedione, BPA = bisphenol A, CAMP = cyclic adenosine monophosphate, CRH = coricotropin-releasing hormone, 1,25-$(OH)_2D_3$ = 1,25-dihydrovitamin D3, DES = diethylstillbestrol, DHT = dihydrotestosterone, DPB = Di-n-butyl phthalate, DHA = dehydroascorbic adic, E1 = estrone, E2 = estradiol, EGF = epidermal growth factor, FGF = fibroblast growth factor, FSH = follicle-stimulating hormone, hCG = human choriongonadotropin , HO1 = heme oxygenase 1, IL = interleukin, MXC = methoxychlor, PMA = phorbol 12-myristate 13-acetate, T = testosterone, TCDD = ,3,7,8-Tetrachlorodibenzo-p-dioxin, TGF = transforming growth factor, TNF = tumor necrosis factor, VPA = valproic acid

Table 5. Preclinical models applied to test HSD17B1 inhibitors *in vivo*

SUMMARY OF STUDIES REPORTING HSD17B1 INHIBITOR TESTING *IN VIVO*				
***In vivo* model**	**Disease induction**	**Intervention**	**Main outcomes**	**Reference**
HSD17B1-transfected endometrial cancer tumors on chicken chorioallantoic membrane	Cancer cells in Matrigel grafted on chicken chorioallantoic membrane	6-day topical administration of 0.1 nM E2, E1 or E1 + 0.1-2.5 µM HSD17B1 inhibitor***	Reduced expression of E2-induced cyclin A and Ki-67 proliferation marker in tumors	(Konings et al. 2018)
HSD17B1TG mammary epithelium grown in wild type female mammary fat pad	Mammary gland lesions induced by high mammary epithelial HSD17B1 expression	4-week administration of HSD17B1 inhibitor*** (10 mg/kg/d, *s.c.*)	No significant change in the mammary lesion number or epithelial cell proliferation.	(Jarvensivu et al. 2018)
ERELuc reporter activity assay in adult female gonadectomized BiTG mice	None	5-day administration of vehicle, E1 (0.3 µg/kg/d, *s.c.*) alone or in combination with HSD17B1 inhibitor (20 mg/kg/d, *s.c.*) #	Reduced E1-induced ERELuc reporter activity in the liver of HSD17B1 inhibitor-treated mice.	(Jarvensivu et al. 2015)

Uterotrophic assay in immature ERELuc reporter-expressing HSD17B1 BiTG mice	None	5-day administration of E1 (0.3 µg/kg/d, *s.c.*) alone or in combination with HSD17B1 inhibitor (25 mg/kg/d, *s.c.*)***, #	Reduced uterine weight, ERELuc reporter activity and proliferation of glandular endometrial epithelial cells in HSD17B1 inhibitor-treated mice.	
Female marmoset monkeys with endometriosis	Non-invasive and invasive endometrial reflux-induced endometriosis	4-week daily oral HSD17B1 inhibitor## treatment.	Decreased pain-associated behavior (increased social and self-grooming activity, comfort behavior and activity) in inhibitor-treated monkeys.	(Arnold and Einspanier 2013)
Gonadectomized athymic mice with subcutaneous T47D breast cancer xenografts	15-day induction of tumor growth with daily *s.c.* E1 injections (0.1 µg/mouse).	32-day administration of E1 (0.1 µg/mouse/d, *s.c.*) + vehicle or HSD17B1 inhibitor (PBRM; 250 µg/mouse/d, *s.c.*)	Reduced tumor size in E1 + HSD17B1 inhibitor-treated mice compared to E1-treated mice.	(Ayan et al. 2012)
HSD17B1TG female mice	High HSD17B1 expression-induced endometrial hyperplasia	6-week administration of HSD17B1 inhibitor** in osmotic minipumps (10 mg/kg/d, *s.c.*)	Completely reversed endometrial hyperplasia.	(Saloniemi et al. 2010)
Intact adult MMTV-HSD17B1TG male and female mice	None	HSD17B1 inhibitor* (25 mg/kg, *i.p.*) administered 10 or 60 min prior to single dose *i.v.* administration of [^{3}H]E1 (35 µg/kg). Blood was collected for [^{3}H]E1/[^{3}H]E2	Reduced proportion of [^{3}H]E2 in blood of [^{3}H]E1-exposed males. Similar trend observed in females.	(Lamminen et al. 2009)

		analysis 2 min after exposure.		
Gonadectomized athymic mice with subcutaneous T47D breast cancer xenografts	35-day induction of tumor growth with daily *s.c.* E1 injections (0.05 or 0.1 µg/mouse)	28-day administration of E1 (0.05 or 0.1 µg/mouse/d, *s.c.* + vehicle or HSD17B1 inhibitor (STX1040; 20 mg/kg/d, *s.c.*)	In both settings, reduced tumor size in E1 + HSD17B1 inhibitor-treated mice compared to E1-treated mice.	(Day et al. 2008)
	21-day induction of tumor growth with E1 pellet (0.001, 0.01 or 0.025 mg/90-day release).	28-day administration of vehicle or HSD17B1 inhibitor (STX1040; 20 mg/kg/d, *s.c.*) to mice with E1 pellets (0.025 mg/90d)		
Intact athymic mice with subcutaneous HSD17B1-transfected MCF7 breast cancer xenografts.	7-day induction of tumor growth with daily *s.c.* E2 injections (1 µmol/kg).	4-week administration of E1 (0.1 µmol/kg/d) + vehicle or HSD17B1 inhibitor (B10720511, B10721325, B10729512, B10720440 or B10715817; 5 µmol/kg/d) in *s.c.* osmotic minipumps.	Dose-dependent reduction in tumor size in HSD17B1 inhibitor-treated mice compared to vehicle-treated mice.	(Husen et al. 2006b)
		4-week administration of E1 (0.1 µmol/kg/d) + B10720511 (0.3, 1, 3, or 10 µmol/d) in *s.c.* osmotic minipumps.		
Gonadectomized athymic mice with subcutaneous HSD17B1	7-day induction of tumor growth with daily *s.c.* E2	4-week administration of E1 (0.1 µmol/kg/d, *s.c.*) +	Reduced tumor size in HSD17B1 inhibitor-treated	(Husen et al. 2006a)

transfected MCF7 breast cancer xenografts.	injections (1 µmol/kg).	vehicle or HSD17B1 inhibitor (B10721325, 5 µmol/kg/d) in *s.c.* osmotic minipumps or ICI 182,780 (179 mg/kg, *s.c.*, once per week).	mice compared to vehicle. Further reduction in tumor size to the level of non-E1 supplemented controls with ICI treatment. Increased proportion of apoptotic cells in the tumors of inhibitor and ICI treated mice.

* Compound 50 in Messinger et al. 2009
** Compound 49 in Messinger et al. 2009
*** Compound 21 in Messinger et al. 2009
# Steroidal core inhibitor (unpublished structure)
Inhibitor not specified