Chapter 4
Cancer of Reproductive System: Receptors and Targeting Strategies

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Abstract Carcinogenesis in the different organs of the reproductive system, particularly, prostate, ovarian, and cervical tissues, involves aberrant expression of various physiological receptors belonging to different superfamilies. This chapter provides insights into the physiological receptors that are associated with the genesis, progression, metastasis, management, as well as the prognosis of the cancers of the male and female reproductive systems. It also highlights the structural and binding characteristics of the highly predominant receptors, namely, androgen, estrogen, progesterone, and gonadotropin-releasing hormone (GnRH) receptors, which are overexpressed in these cancers and discusses various strategies to target them.

Keywords Reproductive · Cancers · Prostate · Ovarian · Cervical · Receptors · Structure · Binding · Target

Abbreviations

5-A DHT	5A-di-hydro testosterone
AD	Adenovirus
ADC	Antibody–drug conjugates
AIs	Aromatase inhibitors
ARE	Androgen response elements

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BPH	Benign prostate hyperplasia
CDK	Cyclin-dependent kinase
CNS	Central nervous system
CRPC	Castrate-resistant prostate cancer
DBD	DNA-binding domain
DOX	Doxorubicin
E2	Estradiol
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EOC	Endometrial ovarian cancer
ER	Estrogen receptor
ERE	Estrogen response elements
FSH	Follicle-stimulating hormone
FSHR	Follicle-stimulating hormone receptor
GLU	Glutamate
GNRH	Gonadotropin-releasing hormone
GNRHR	Gonadotropin-releasing hormone receptor
GPCR	G-protein-coupled receptor
GPER	G-protein estrogen receptor
HER-2	Human epidermal growth factor receptor-2
HPG	Hypothalamic–pituitary gonadal (axis)
HPV	Human papilloma virus
HRE	Hormone response elements
HSP	Heat shock proteins
i.m.	Intramuscular
LBD	Ligand-binding domain
LBP	Ligand-binding pocket
LH	Luteinizing hormone
LHR	Luteinizing hormone receptor
mAbs	Monoclonal antibodies
MCRPC	Metastatic castrate-resistant prostate cancer
NLS	Nuclear localization signal
NTD	N-terminal transcription regulational domain
P4	Progesterone
PR	Progesterone receptor
PRB	Retinoblastoma protein
PRE	Progesterone response elements
PSA	Prostate-specific antigen
PSGR	Prostate-specific G-protein-coupled receptor
PSMA	Prostate-specific membrane antigen
PSMAA	Prostate-specific membrane aptamers
RES	Reticulo-endothelial system
RP2D	Recommended phase 2 dose

s.c.	Subcutaneous
SAR	Structure–activity relationships
SARM	Selective androgen receptor modulators
SCID	Severe combined immunodeficiency
SERM	Selective estrogen receptor modulators
SMA	Styrene–maleic scid
SMA-RAL	SMA-encapsulated raloxifene
SPRM	Selective progesterone receptor modulators
TMD	Transmembrane domain

1 Introduction: Reproductive System-Related Cancers

Cervical and ovarian cancers are the fourth most and the seventh most common cancers in women, with a global prevalence of approximately 3.7 percent and 1.7 percent, respectively [1–3]. The prostate cancer is considered as the fifth leading cause of cancer-associated mortality in men, with a global prevalence of about 7.9 percent [3, 4]. The risk factors for cancers related to reproductive system include but not limited to endogenous factors such as genetic history, race, aging, hormonal imbalance, and exogenous factors such as inappropriate diet, unhealthy lifestyle, and environmental and occupational factors. Moreover, cervical cancer risk factors are extended to the infection of human papilloma virus (HPV), extended usage of contraceptives, age of menarche and menopause, unsafe sexual activities such as sexual intercourse at an early stage and multiple sexual partners [1, 5–12]. This chapter provides a detailed overview of the structural, pharmaceutical, and clinical aspects of the agents discovered to target the dominant receptors involved in the development, treatment, and prognosis of the reproductive neoplasia.

2 Overview: Receptors Associated with the Cancers of the Reproductive System

Table 4.1 lists the receptors that are ubiquitous in various cancers of the reproductive system, specifically during their prognosis, diagnosis, progression, and therapy.

The subsequent discussion is focused on four principal receptors that display a significant expression pattern during the genesis, diagnosis, treatment, and prognosis of the reproductive neoplasia.

Table 4.1 Receptors associated with the prognosis, diagnosis, progression, and therapy of the cancers of the reproductive system

Type of receptors	Cervical cancer	Ovarian cancer	Prostate cancer
Ion channel receptors (inotropic)	P2 receptors: P2X4, P2X7 [13–15]	P2 receptors: P2X7 [13, 14]	P2 receptors: P2X4, P2X5, P2X7 [13, 14] NMDA (N-methyl-D-aspartate) receptor [16] GABAa receptor [17]
G-protein-coupled receptors (GPCRs) (metabotropic)	Endothelin-1: (ET_AR) [18–20] Protease-activated receptor-2 (PAR-2) [21] Gastrin-releasing peptide receptor (GRPR) [22, 23] G-protein-coupled estrogen receptor-1 (GPER-1) – prognostic maker for early-stage cancer [7] Folate receptor subtype alpha (FRα) [24]	Endothelin-1: (ET_AR) [19, 25, 26] Protease-activated receptor-1 and 2 (PAR 1 and 2) [27, 28] β-Adrenergic receptor [29] Gastrin-releasing peptide receptor (GRPR) [30, 31] G-protein-coupled estrogen receptor-1 (GPER-1) [32, 33] Folate receptor – FRα and Reduced Folate Carrier (RFC) [34] Follicle-stimulating hormone receptor (FSHR) Luteinizing hormone receptor (LHR) Gonadotropin-releasing hormone receptor (GnRHR) Thyroid-stimulating hormone receptor (TSHR) Kisspeptin receptor Angiotensin II type 1 receptor [2] Serotonin (5-HT) receptors – 5-HTR1A, 5-HTR1RB, 5-HTR2B, 5-HTR4 [35]	Endothelin-1: (ET_AR) [19, 36, 37] Protease-activated receptor-1, 2, and 4 (PAR-1, 2, and 4) [38–40] β-Adrenergic receptor [29, 41] Gastrin-releasing peptide receptor (GRPR) [31, 42] G-protein-coupled estrogen receptor-1 (GPER-1) [33] Prostate-specific G-protein-coupled receptor (PSGR)-PSGR2 [43, 44] G-protein-coupled receptor-158 (GPR158) [45] Lysophosphatidic acid (LPA)-1 receptor [46] Gonadotropin-releasing hormone receptor (GnRHR) [47] Serotonin (5-HT) receptors – 5-HTR1A, 5-HTR1RB, 5-HTR2B, 5-HTR4 [48, 49]

(continued)

Table 4.1 (continued)

Type of receptors	Cervical cancer	Ovarian cancer	Prostate cancer
Tyrosine kinase receptors	Human epidermal growth factor receptor (HER-2)/neu [50] Epidermal growth factor receptor (EGFR) [51] Insulin-like growth factor-I receptor (IGF-IR) [52] Vascular endothelial growth factor (VEGF) receptor [53] Prolactin receptor (PRLR) [54] Hepatocyte growth factor/(cMET) [55] Fibroblast growth factor receptor (FGFR) [56]	HER-2/neu receptor [57] Epidermal growth factor receptor (EGFR) [58] Insulin-like growth factor-I receptor (IGF-IR) [59] Vascular endothelial growth factor (VEGF) receptor [53] Hepatocyte growth factor/(cMET) [60] Fibroblast growth factor receptor (FGFR) [61]	HER-2/neu receptor [62] Epidermal growth factor receptor (EGFR) [63] Insulin-like growth factor-I receptor (IGF-IR) [64] Vascular endothelial growth factor (VEGF) receptor [65] Hepatocyte growth factor/(cMET) [60] Fibroblast growth factor receptor (FGFR) [66]
Nuclear receptors	Estrogen receptor (ERα and ERβ) Progesterone receptor (PR): PR-A, PR-B [1] Vitamin-D receptor (VDR) [67] Retinoic acid receptor β [68]	Estrogen receptor (ERα and ERβ) Progesterone receptor (PR): PR-A, PR-B [1, 69] Androgen receptor (AR) Vitamin-D receptor (VDR) [67] Retinoic acid receptor [70]	Androgen receptor (AR) [71] Estrogen receptor (ERβ) [72] Progesterone receptor (PR) [73] Peroxisome proliferator-activated receptor-Gamma (PPARγ) [74]

3 Predominant Receptors in Reproductive System-Related Cancers

3.1 Nuclear Receptors

Nuclear receptors comprise a family of transcription factors that get activated due to the binding of the lipophilic ligands, to carry out reproduction, development, homeostasis, and metabolism. They act by responding to the signals generated by the steroid hormones and regulate the expression of the target genes [75–77].

3.1.1 Steroid Sex Hormone Receptors

The organs of the reproductive system serve as the primary sites of action of sex steroid hormones, such as the estrogen, progesterone, and androgen. These hormones are responsible for mediating the developmental activities and physiological

functions of the male and female reproductive systems. They exert their functions through the action of steroid hormone receptors, namely, the estrogen (ER), progesterone (PR), and androgen (AR) receptors, respectively. Aberrations in their expression and/or in the factors regulating them, termed as coregulators, lead to either activation or suppression of their transcription machinery, eventually impacting their physiological functions. These abnormalities trigger a cascade of pathological changes in vivo, thereby resulting into carcinogenesis [78, 79].

ER-subtype α (ERα) and PR receptors play a pivotal role in the pathophysiology of cervical cancer. The PRs were found to exhibit tumor-suppressive properties in cervical cancer [1, 7]. In the case of ovarian malignancy, ERα expression provided a better prognosis, while the role of ERβ was insignificant. On the other hand, an elevated PR expression was observed to improve the survival rate in patients with endometrial ovarian cancer (EOC) [80]. The activity of AR has been closely linked to the prostatic carcinogenesis. The biochemical pathway of AR, the principal regulator of prostatic cancer, is perturbed during the carcinogenesis. Castration-resistant prostate cancer (CRPC), an advanced stage of the disease which is nonresponsive to hormone deprivation therapy, occurs due to increase in sensitivity of the AR to the agonists, mutations in the receptor, ligand-independent activation of the ARs, etc. [71]

3.2 G-Protein-Coupled Receptors

3.2.1 Gonadotropin-Releasing Hormone Receptor (GnRHR)

GnRH-I, produced in vivo, by the GnRHR (located in the hypothalamus) stimulates the secretion of the gonadotropins, namely the luteinizing hormone (LH) and the follicle-stimulating hormone (FSH), which further regulate the in vivo levels of sex hormones [81]. The GnRHR is also expressed in the CRPC [82]. Primary cultures of ovarian carcinomas and biopsy specimens of malignant ovarian tissue have revealed the predominant expression of the GnRHR receptor (>80%), signifying its role in the genesis of malignancy and metastasis. The GnRHR has also been speculated to be associated with the early phases of ovarian carcinogenesis, including cell migration and invasion [83]. It was observed that administration of GnRH-1 agonists and antagonists lead to the downregulation and inactivation of GnRHR, respectively. As a result, the GnRH agonists cause inhibition of cell proliferation, metastasis, and angiogenesis. Moreover, the GnRH antagonists also possess antineoplastic activity [81, 82]. Thus, exploration of the structure and regulation of the GnRHRs in cancers of the reproductive system may enhance their applicability, as a target receptor, for the discovery of new-age anticancer therapeutics.

Understanding the structure and the binding chemistries of these receptors and reviewing the potential of targeting it may pave the way to the discovery of the breakthrough anticancer therapies in the near future.

4 Predominant Receptors in Cancers Related to Reproductive System: Structural Attributes

4.1 Androgen Receptor

Androgen receptor (AR), a 110-kDa protein, is a ligand-activated transcription factor belonging to the family of steroid hormone nuclear receptors [71]. AR, expressed in prostate, is activated by binding of endogenous androgens, such as testosterone and 5α-dihydrotestosterone (5 α-DHT). Functional AR is responsible for in vivo male sexual differentiation and occurrence of pubertal changes [84].

This receptor mediates normal growth and development of the prostate gland and also plays a vital role in the prostatic carcinogenesis and its progression to an androgen-independent disease. Androgen-independent stage of prostate cancer (e.g., CRPC) has been observed due to the activation of the AR receptor by overexpression of gene and cofactors, gene mutations, splice variants, and intracrine synthesis of androgen [85, 86]. In addition, AR is also expressed in the different subtypes of ovarian and cervical cancers [87, 88].

4.1.1 Androgen Receptor: Recognition Domain and Receptor Pathway

The AR modular protein consists of four distinct domains, namely, the ligand-binding domain (LBD), the hinge domain, the DNA-binding domain (DBD), and the N-terminal transcriptional regulation/amino-terminal domain (NTD). NTD is the most variable region, whereas DBD and LBD are highly conserved among different receptors of the steroid hormone nuclear receptor family. The LBD, the key recognition domain of AR, is arranged in three layers and comprises eleven α-helices, particularly, H1–H11, except H2, which results into formation of an antiparallel "α-helical sandwich." The ligand-binding pocket (LBP) is formed by H5, C-terminal of H10 and H11, and N-terminal of H3. The activation function (AF)-1, located at the N-terminal, is not conserved in the sequence and is ligand-independent, whereas AF-2, at the C-terminal, is conserved and ligand-dependent. The nuclear localization signal (NLS) is located between the DBD and the hinge region [71, 89, 90].

The Genomic Pathway of AR

Unbound AR exists in an inactive state in the cytoplasm, in complexation with the heat shock proteins (HSP) such as HSP90. Upon binding to a ligand/agonist, it gets activated and dissociates from the HSP and undergoes dimerization and phosphorylation. Binding of an agonist leads to the formation of the AF-2 region on the surface of LBD. Upon ligand binding, AF-2 interacts with the amino-terminal motifs of the receptor, which leads to an establishment of N/C intradomain crosstalk, thereby leading to receptor stabilization, enhanced DNA-binding affinity, and

reduced ligand dissociation, a phenomenon exclusively observed in the AR, unlike other steroid receptors. AF-2 domain also recruits coregulatory proteins to an activated AR, thereby contributing to its overall function. H12, the core structure of AF-2, acts as a lid to close LBP, upon binding of the agonist. Further, the NLS gets exposed upon the ligand/agonist binding and interacts with importin-α. This leads to translocation of AR from cytoplasm to the nucleus. DBD facilitates interaction of the translocated receptor with the DNA at specific recognition sites. These sites, located in the promoter and enhancer regions of the AR target genes, consist of consensus sequences and are termed as androgen response elements (ARE). Access of AR to the target chromatin requires concerted action of certain transcription factors. AF-1 and AF-5 of NTD mediate the transcriptional activity by recruitment of coactivator complexes and transcription machinery, essential to regulate the expression of the target genes. Selective recognition of specific ARE sequences is regulated by the ligand-binding and/or presence of other transcription factors [84, 89–91]. Figure 4.1a provides a schematic layout of the structure of the steroid receptor (SR) and its pathway of transactivation after binding of the ligand.

4.1.2 Ligands and Their Structure–Activity Relationships (SAR) for Selective Binding to AR

Ligands modulate their action by binding to the LBP of LBD. The AR is capable to accommodate a large variety of ligands by modifying the volume of LBP [71]. Testosterone (Fig. 4.2a) and DHT (Fig. 4.2b) are the physiological ligands of the AR [89]. Carbon atoms of the testosterone skeleton have been numbered in order to provide basis for the SARs with various ligands and their derivatives [71]. Synthetic derivatives of testosterone have been prepared to enhance oral bioavailability. It is essential for the ligand (natural/synthetic) to contain a steroidal skeleton for retaining the androgenic activity. Hydrophobic amino acid residues in the LBP interact with the steroid scaffold. A/B ring junction usually has “trans” stereochemistry. 17β-OH atom is essential for ligand–receptor interaction via formation of a hydrogen bond with the amino acid residues [71, 89].

Fig. 4.1 (**a**) Schematic of the structure and genomic pathway of the Steroid Receptor (SR) activated upon binding of the ligand (e.g., hormone). Binding of the ligand causes activation of the HSP-90-bound SR that undergoes nuclear translocation, dimerization, and then binds to the hormone response elements (HRE) by the action of cofactors/coactivators, thus resulting into transactivation and transcription of the target genes. The enlarged view of the SR reveals different structural domains, namely, N-terminal domain (NTD), DNA-binding domain (DBD), Hinge region (H), and ligand-binding domain (LBD), wherein each domain is capped by N-termini and C-termini amino acid residues. Presence of NLS, AF-1, and AF-2 domains has also been indicated. (**b**) Schematic representation of GnRHR and intracellular pathway activated on binding of GnRH. Binding of the ligand activates the receptor. The latter binds to GTP-linked proteins, or G-proteins. Gαq/11, a subunit of G-proteins, activates phospholipase C, which then hydrolyzes phosphatidylinositol-4,5-bisphosphate (PIP2) to inositol triphosphate (IP3) and diacylglycerol (DAG). DAG activates protein kinase C (PKC), further leading to cascade of intracellular events, operating through activation of phospholipase A2, ultimately leading to Gonadotropin biosynthesis and release

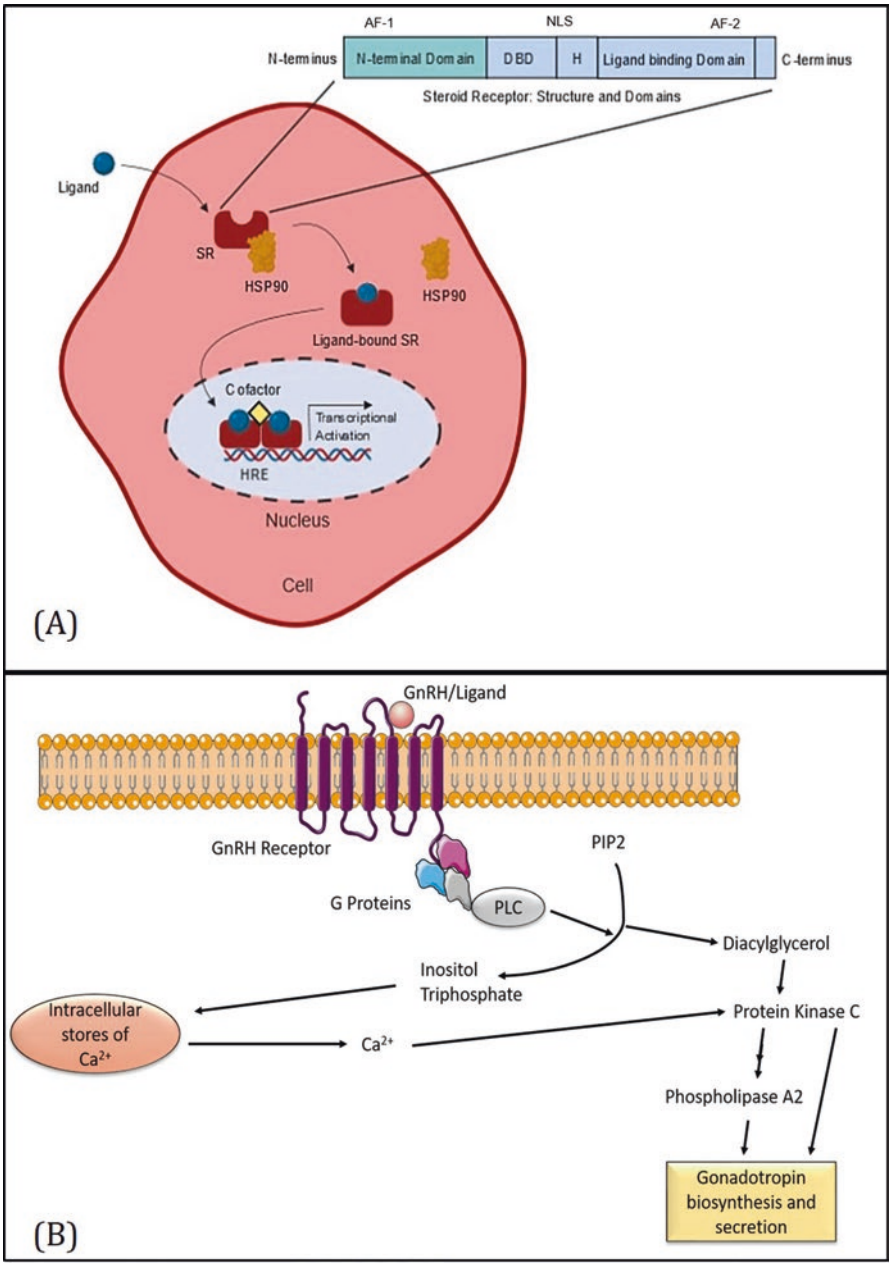

Fig. 4.1 (Caption on p. 116)

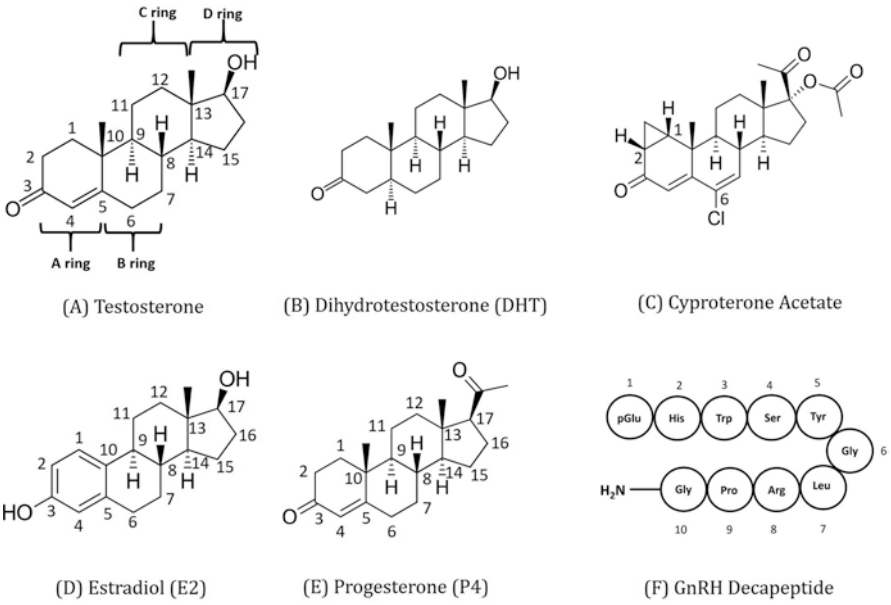

Fig. 4.2 Structure of ligands/chemical agents and action on the predominant receptors of cancers of the reproductive system. Carbon atoms and hydrophobic rings have been numbered wherever necessary. (**a**) Testosterone, (**b**) Dihydrotestosterone, (**c**) Cyproterone acetate, (**d**) Estradiol (E2), (**e**) Progesterone (P4), and (**f**) GnRH decapeptide

4.2 Estrogen Receptor

Estrogens naturally occur in three different forms in females, namely, estradiol (E2) (Fig. 4.2d), estriol, and estrone. It exerts its action through the estrogen receptors (ERs), which belong to the steroid hormone superfamily of nuclear receptors. ERs, occurring in two forms, ER-α and ER-β, act as ligand-activated transcription factors, upon binding to the endogenous ligands [92–94]. Expression of estrogen and its receptors have been very well documented in prostate, ovarian, and cervical cancers. ER-α and ER-β have been reported to play oncogenic and antioncogenic roles in the pathogenesis of prostate cancer. The aberrant expression of the enzymes involved in steroid biosynthesis and metabolism, such as aromatase and 5-α reductase, has also been implicated in prostatic malignancy [72, 95]. This chapter will further provide insights into the structural aspects of the receptor and its SAR with the ligands.

4.2.1 Recognition Domain and Receptor Pathway of ER

ER-α (66-kDa protein) is predominantly expressed in the reproductive tract, whereas ER-β (54-kDa protein) primarily occurs in the vascular endothelial cells, bones, and male prostatic tissues. The ER receptor consists of an NTD, DBD,

hinge region, and LBD. The NTD stimulates transcription from particular estrogen-responsive promoters via AF-1. DBD binds to estrogen response elements (ERE) in the target DNA, while the hinge region contains nuclear NLS. The LBD and AF-2 activate the gene expression in response to ligand binding. The classical genomic pathway results in the formation of estrogen-dependent, nuclear ER homo- or heterodimers, such as ER-α/ER-α, ER-β/ER-β, and ER-α/ER-β, respectively. Further, these dimers subsequently bind to the estrogen response element (ERE) sequences located in the promoter region of estrogen-responsive genes, resulting in the recruitment of coregulatory proteins (coactivators or corepressors) to the promoter. This leads to either an enhancement or reduction in the mRNA levels, further impacting the production of associated proteins and eventually the physiological response [89, 96].

4.2.2 Ligands and Their Structure–Activity Relationships for Selective Binding to ER

A vast array of compounds acting as ligands for the ER-α and ER-β receptors have been classified as endo-estrogens (E2), phytoestrogens (Resveratrol), xenoestrogens (Mestranol), metalloestrogens (copper (Cu^{2+}), etc. [89, 97, 98].

Recognition of the binding of endo-estrogen (E2) to ER is achieved partly by intermolecular hydrogen binding and van der Waals interactions with the receptor [97]. The aromatic A ring, C-3 and 17β hydroxyl groups and the distance between them, and planar hydrophobic structure are essential for estrogenic activity. On the other hand, substitution at C-1, hydroxylation at C-6, 7, and 11, removal of oxygen from C-3 or C-17, and epimerization of 17-β-hydroxyl group of E2 to α-configuration lead to reduction in the activity [89, 99].

4.3 Progesterone Receptor

Progesterone (P4; represented in Fig. 4.2e) and progesterone receptors (PRs) are necessary for the development of hormone-responsive tissues such as breasts and other organs of the reproductive tract. It is responsible for ovulation, embryo implantation, pregnancy, development of the mammary gland, and sexual differentiation and behavior. The hormone inhibits the proliferative action of estrogen in the reproductive tissues, such as endometrium and ovary, thus preventing them from undergoing neoplastic transformation [100, 101]. PRs, existing as two isoforms, namely PR-A ((molecular weight of 94 kDa) and PR-B (molecular weight of 114 kDa), are ligand-activated transcription factors, belonging to the superfamily of steroid hormone nuclear receptors. PR-B is referred to as full length and dominant receptor, while PR-A is the N-terminal truncated version [102, 103]. Both the isoforms suppress proliferation of the prostate stromal and cervical cancer cells [1, 104]. PR overexpression is associated with favorable prognosis in women with ovarian malignancies [105].

4.3.1 Recognition Domain and Receptor Pathway of PR

The PR receptors share common structural elements with other steroid receptors, namely, NTD, DBD, hinge region, and LBD. The NTD is responsible for ligand-independent transcriptional activation and harbors a highly variable AF-1 domain. The DBD binds to the progesterone response elements (PREs) located in the target DNA. The hinge region contains NLS, while the LBD and a highly conserved AF-2 domain are responsible for the ligand-mediated transactivation of the gene expression, via the genomic pathway. The LBD or the primary recognition domain comprises a hydrophobic LBP, to facilitate ligand binding. The genomic pathway operates on binding of P4, which causes conformational change in the PR, thereby transforming it into an active transcriptional factor. As a result, receptor phosphorylation occurs and the PR undergoes dimerization (homo/hetero) and nuclear translocation, to further interact with the PREs. This also leads to the recruitment of coactivators that mediate gene transcription. It has been reported that PR-A and PR-B possess opposite transcriptional activities and the overall response of P4 is dependent on the relative in vivo levels of PR-A and PR-B. 5α-reductase and 20α-hydroxysteroid dehydrogenase are responsible for the metabolic conversion of P4 to a more active or less active form, before interaction with the receptors in the target cells [89, 102, 106].

4.3.2 Ligands and Structure–Activity Relationships for Selective Binding to PR

P4 is an endogenous ligand of the PR receptors. The progestin activity is confined to the molecules having a steroid nucleus. The synthetic progestins have been categorized into two classes, namely, the androgens (19-norandrostane or estrane derivatives), and 17 α-hydroxyprogesterones. In case of the compounds belonging to the androgen category, 17α-substituents like ethyl, methyl, etc., lead to increase in the oral bioavailability (e.g., Ethisterone). Removal of the methyl group at C19 position and chlorination at C21 or methylation at C18 provided norethisterone, whose activity was further enhanced by chlorine substitution at C21 or by the addition of methyl group at C18 (e.g., Norgestrel). Acylation of 17β-hydroxyl group of Norethisterone extended the duration of its action. Synthetic progestins include medroxyprogesterone acetate and norethisterone (first generation), norgestrel and levonorgestrel (second generation), etonogestrel and nosgestimate (third generation), drospirenone and trimegestone (fourth generation), etc. [89].

4.4 Gonadotropin-Releasing Hormone Receptor (GnRHR)

The GnRH (Fig.4.2f) is a decapeptide that plays a pivotal role in regulating the reproductive functions by functioning through the hypothalamic–pituitary gonadal (HPG) axis. The action of GnRH is mediated by the action of GnRHR, which

belongs to the rhodopsin-like GPCR superfamily. GnRHR is expressed in various reproductive cancers, such as the prostate, ovarian, endometrial, and the breast cancer, as well as the nonreproductive cancer types. In these tumors, the GnRH functions as a paracrine–autocrine growth factor and displays a strong anticancer activity. The GnRHR (for 3D structure, refer to Flanagan C.A. et al.) consists of seven transmembrane (TM) domains, as well as an extracellular amino-terminal domain that contains 35 amino acids, along with two putative glycosylation sites. However, it lacks the carboxy-terminal cytoplasmic tail resulting in slow internalization and desensitization of the receptor. The membrane-spanning segments are highly conserved, while the loops and the termini constitute to be the variable regions [47, 82, 107, 108].

4.4.1 Gonadotropin-Releasing Hormone Receptor: Recognition Domain and Receptor–Ligand Interactions

The receptor (R) exists in an equilibrium between an inactive R, which does not activate G proteins and is stabilized by an antagonist, and an active R^* conformation, which activates G proteins and is stabilized by agonists, depending on the presence or absence of the ligand. The ligands of the receptor interact with the variable, extracellular half of the receptor molecule. The membrane-spanning receptor domain transmits the signal generated upon ligand binding to the cytosolic receptor surface, which further interacts with the G protein. The GnRHR must exist in a silent state that does not activate the G protein, in order to transduce the signals mediated by agonists across the cell membrane. Binding of the agonist causes transition from the silent state and leads to the binding and activation of G proteins, situated on the opposite side of the cell membrane. Thus, agonists like GnRH act as allosteric activators of the receptor. The primary features of the inactive form of the receptor include closed G-protein-binding pocket, a hydrogen-bonding network, and a hydrophobic barrier. Binding of the ligand activates the receptor, causing rotation and change in the interfaces of specific TM segments, leading to opening of the hydrophobic barrier, movement of specific amino acid residues toward the interior of the TM bundle, and ultimately opening of the cytoplasmic surface cleft that allows contact and binding of the G-proteins [108]. The structure of the recognition domain or LBD of the receptor, involved in binding, depends on the type of the ligand such as a neurotransmitter, a glycoprotein hormone, and a peptide. In the case of a neurotransmitter, the TM domains (TMDs) themselves form the LBP to facilitate ligand binding. The amino-terminal domain of the receptor, encompassing the high-affinity ligand-binding site, has been reported to be recognition domain for glycoprotein hormones. A high-affinity binding site for the peptide-based ligands include both extracellular and TM residues [109].

4.4.2 Gonadotropin-Releasing Hormone Receptor Pathway

Binding of the hormone causes coupling of GnRHR to $G_{\alpha q/11}$ protein, which stimulates the phospholipase Cβ (PLCβ) activity. This leads to the enhancement of intracellular levels of inositol triphosphate (IP3) and diacylglycerol (DAG), further causing intracellular mobilization of Ca^{2+} ions and activation of the protein kinase C (PKC). These downstream effects lead to the activation of various signaling pathways, which operate through the MAPK reaction cascade. Phospholipase D and phospholipase A2 are also activated in a sequential manner. These biochemical pathways are vital in eliciting the GnRH-mediated downstream effects, such as gonadotropin synthesis and secretion [47]. Figure 4.1b provides a schematic representation of the GnRHR, a GPCR, and the intracellular pathway activated upon binding of GnRH to the receptor.

4.4.3 Structure–Activity Relationships for Selective Ligand Binding to GnRHR

Amino- and carboxy-terminal residues are critical for receptor binding and activation. The presence of achiral glycine (Gly) or D-amino acids is essential at position 6, to facilitate active conformation in the folded state. His^2, Trp^3, as well as $pGlu^1$ of the GnRH decapeptide possess significant roles in receptor activation. Substitution of amino acid residues located outside the amino-terminal domain is speculated to affect the receptor activation, due to the conformational changes in the ligand that may occur upon binding to the receptor [110].

The subsequent section of the chapter highlights the approaches explored for receptor targeting as well as an overview of mechanisms involved therein.

5 Approaches for Receptor Targeting: Relevance to Cancers of Reproductive System

Table 4.2 provides an overview of drug molecules developed to target receptors predominantly expressed in the cancers of the reproductive system. Fig.4.3 provides a schematic layout of the classification of the agents (ligands, agonist, antagonists, modulators, etc.), either endogenously present and/or synthesized for targeting to the aforementioned receptors.

5.1 Mechanisms of Receptor Targeting and Implications in Cancers of Reproductive System

Several mechanisms employed for targeting receptors predominantly expressed in the cancers of reproductive system have been summarized and supported by relevant case studies in this section.

Table 4.2 Overview of drug molecules developed to target receptors predominantly expressed in the reproductive neoplasia

Sr. No.	Class	Description	Examples	Ref
1	Selective androgen receptor modulators (SARM)	The nonsteroidal compounds, referred to as Selective androgen receptor modulators (SARM), demonstrate weak agonistic or antagonistic activity in prostate cancer, while they exhibit agonistic effects in the peripheral tissues. They consist of four principal pharmacophores, namely, N-aryl propionamide, bicyclic hydantoins, quinolinones, tetrahydroquinoline analogs, benzimidazoles, butanamides, etc. These nonsteroidal compounds were found to be superior to their steroidal counterparts, with respect to their receptor selectivity and pharmacokinetic properties.	Ostarine, LGD2226, BMS564929, etc.	[89, 111]
2	Androgen receptor antagonists	AR antagonists, also referred to as antiandrogens, act by competitive inhibition, thus affecting binding of a ligand to the AR. These agents, extensively used for treating prostate cancer, are structurally classified as steroidal and nonsteroidal compounds as well as reversible and irreversible ligands. Reversible ligands undergo interaction with the AR via noncovalent bonds, such as hydrogen, electrostatic, and hydrophobic bonds, whereas irreversible ligands undergo permanent attachment with the receptors via covalent interactions. Different classes of the steroidal antiandrogens include testosterone and DHT derivatives, synthetic progestins, steroidal sulfonyl heterocycles, 4-Azasteroids and Des-A-steroidal antiandrogens. The nonsteroidal antiandrogens categorized as nitrotrifluorotoluenes, trifluoromethylbenzonitriles, quinoline derivatives, cyclocymopol analogs, phthalimide derivatives, etc., have been studied for their AR antagonistic activities. Peptidomimetic pyrimidines (inhibitors of cofactor binding), sintokamide A and oxindole I (inhibitors of AR transactivation), etc., are some of the few recently reported inhibitors.	*Steroidal antiandrogen:* Cyproterone Acetate (Androcur®) (Fig. 4.2c) *Nonsteroidal antiandrogens:* Flutamide (Eulexin®) and Nilatumide (Nilandron®), Bicalutamide (Casodex®)	[112–118]
3	Natural agents targeted to AR	Drugs isolated from natural products have also been found to have a substantial impact on reducing the growth of prostate cancer. Natural drug products are usually preferred as they are regarded as safe and effective in cancer treatments and exhibit lower side effects than the synthetic counterparts.	Selenium, Soy isoflavones, Epi-brassinolide (EBR), Curcumin, etc.	[119]

(continued)

Table 4.2 (continued)

Sr. No.	Class	Description	Examples	Ref
4	Selective estrogen receptor modulators (SERM)	It includes the agents interfering with the activation of ER receptor and the ones limiting the biosynthesis of the estrogens (e.g., aromatase inhibitors). They bring about conformational changes in the LBD that are slightly different from those triggered by the binding of E2 to the receptor. Change in the orientation and binding pattern of the helices and LBP located in the LBD, as well as inhibition of the recruitment of transcription coactivators, leads to the overall antagonistic effect.	Tamoxifen, Raloxifene, Droloxifene	[89]
5	Antiestrogens	They prevent nuclear translocation of the ligand–ER complexes and interfere with the binding of DBD of ER to the ERE elements located on the chromatin.	Enclomiphene, Zuclomiphene, Fulvestrant (ICI) (Faslodex®)	[89]
6	Aromatase inhibitors (AIs)	They are useful either as a mono or as a combination therapy and act by blocking the synthesis of estrogen by inhibiting the aromatase activity.	Letrozole (Femara®), Anastrozole (Arimidex®)	[120, 121]
7	Selective progesterone receptor modulators (SPRMs)	SPRMs act as partial agonists/antagonists and are majorly employed for emergency contraception, termination of pregnancy, dysmenorrhea, premenstrual syndrome, etc. However, due to the associated safety concerns, their usage has been discontinued.	Asoprisnil, Ulipistal acetate (UPA), Vilaprisan	[122]
8	Progesterone receptor antagonist (PRA)	PRAs or antiprogestins compete with P4 for its receptor and eventually prevent the latter from binding to and activating the receptor.	Mifepristone, Onapristone	[89, 123]
9	GnRHR agonists	They act by interfering with the activities of the epidermal growth factor (EGF) and insulin-like growth factor 1 (IGF-1) and inducing cell apoptosis. These agents are 60 times more potent than the native molecule. They are characterized by prolonged half-life and enhanced receptor binding, in comparison to the natural ligand. These agonists have been utilized to treat advanced prostate cancer along with management of ovarian and endometrial cancers.	Goserelin (Zoladex®), Leuprolide (Eligard®), Leuprorelin (Prostap®), triptorelin (Decapeptyl®), and histrelin (Vantas®)	[47, 82, 124]

10	GnRHR antagonists	Discovered to mitigate the flare phenomenon encountered upon administration of the agonists, these agents bind to the receptor in a competitive manner, without activating the intracellular signaling cascade. They act in a time- and dose-dependent manner, to exhibit a cytotoxic effect on the GnRHR-expressing tumor cells, and their cellular action mimics that of the agonists. Administration of these agents in prostate cancer leads to rapid reduction in the levels of LH, testosterone, DHT, and prostate-specific antigen (PSA). Structurally, the GnRH antagonists involve five or more amino acid substitutions, compared to the natural decapeptide. Alterations at positions 1, 6, and 10 affect the receptor binding, while substitutions at positions 2 and 3 affect the gonadotropin release. Administration of GnRHR antagonists was found to be beneficial, as compared to the combination therapy of GnRH agonists and antiandrogens for prostate cancer. The GnRH antagonists offer several benefits over the agonists, which include absence of flare, rapid pituitary downregulation periods, possibility of being administered alone, and availability in depot or subcutaneous formulations. Thus, they are safer and cost-effective, and at the same time can be targeted directly to the primary and secondary tumor cells. This is anticipated to achieve speedy recovery of the pituitary–gonadal function after withdrawal of the treatment.	Cetrorelix, Abarelix, Degarelix, and Ganirelix (Commercially available); Antarelix, Antide, Azaline B, Acyline, and Ozarelix (under clinical investigation)	[47, 82, 125]

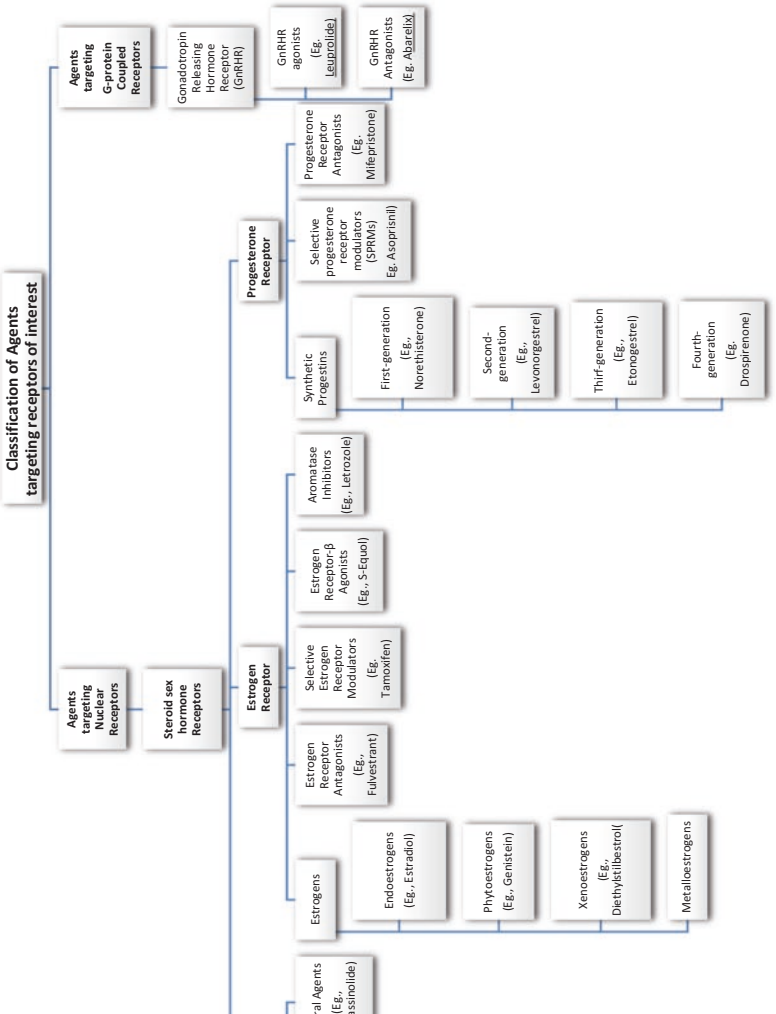

Fig. 4.3 Overview of the classification of several classes of agents, either endogenous or synthesized and used for targeting nuclear receptors and GPCRs, predominantly expressed in the cancers of the reproductive system

5.1.1 Prodrug Approach

The limitations of chemotherapy, such as toxicity and lack of selectivity, can be addressed with different approaches that selectively target the existing drugs to the malignant cells and through the development of nontoxic forms of anticancer agents, which may be specifically activated in the tumor tissues. Selective activation of prodrugs into active anticancer agents, in the vicinity of tumor tissues, can be mediated either by metabolic activity or by spontaneous chemical breakdown. Investigations have been carried out for targeting advanced mCRPC by prodrug approach by means of targeting prostate cancer-specific antigens such as prostate-specific antigens (PSA), prostate-specific membrane antigens (PSMA), CD147, heat shock proteins (HSPs), leutinizing hormone-releasing hormone (LHRH) receptor, epithelial cell adhesion molecules, etc., and prostate-specific enzymes such as cathepsin or matrix metalloproteinase. Numerous PSMA-targeting molecules, which include monoclonal antibodies (mAbs), antibody–drug conjugates (ADCs), antibody fragments (Fabs), peptides, and aptamers, have been developed in the form of prodrugs or nanoparticles. In recent times, a prodrug, namely vinblastine-N-oxide (CPD100), was developed for the treatment of ovarian cancer by Cascade Prodrug, a US-based pharmaceutical company. This compound, formulated as sphingomyelin-cholesterol liposomes, is converted into its parent compound, vinblastine, under hypoxic conditions. This formulation was found to be highly successful in the preliminary studies and if successful in clinical trials, it will be the first-of-its-kind of chemotherapeutic agent to demonstrate anticancer activity due to the hypoxic microenvironment present in the solid tumors [126–128].

5.1.2 Indirect Targeting of the Receptor

Malignancies specific to prostate gland can also be controlled by indirect targeting of AR-targeted drugs such as agonists, antagonists, partial agonists, and antagonists. Indirect targeting approach can also be considered such as targeting small molecules like 17α-hydroxylase involved in the de-novo synthesis of androgens by drugs such as Abiraterone. Abiraterone, in combination with prednisone, was approved in 2012 as the first-line therapy against mCRPCs, before commencing the administration of the conventional chemotherapy. Tamoxifen is the oldest and the most extensively studied SERM. It is a prodrug with low ER affinity, and gets converted into active metabolites such as endoxifen or afimoxifene through metabolism in the liver. These active metabolites demonstrate 30–100 times greater affinity toward the target receptors, as compared to tamoxifen. Substances involved in the synthesis of estrogen, such as aromatase, can also be considered as alternative targets for the treatment of ovarian cancers. The AIs blocks the protein involved in estrogen synthesis, but their usage is limited for the postmenopausal women, as they do not inhibit estrogen synthesis in the ovaries of the premenopausal women. Fulvestrant (Faslodex®), Anastrozole (Arimidex®), Letrozole (Femara®), and Exemestane (Aromasin®) are examples of the AIs, which are useful either as a monotherapy or combinatorial therapy, during the treatment of ovarian cancer [121, 129–131].

5.1.3 Molecular-Based Targeting Approach: Gene Therapy

Gene therapy has been explored as one of the advanced ER-targeting strategies. Recently, an innovative effort provided a strong confirmation that enhanced estrogen signaling is responsible for the growth of the cervical tumor. Enhanced expression of Cyclin D1, ERs, and aromatase is significantly associated with the tumor growth. Hence, blocking the estrogen pathway, particularly to decrease the ER activity, can be a rational approach to activate p53 and retinoblastoma protein (pRb), along with lowering the expression of HPV E6 and E7. This approach has been utilized to block ER-mediated tumor growth in cervical cancer cells, by transfection using adenovirus (AD) as a gene carrier [132].

5.1.4 Novel/Nano Drug Delivery Systems

Different approaches of drug delivery are being employed to target receptors expressed in reproductive neoplasia. Promising results of raloxifene in clinical trials has suggested for an improvement in the efficacy of this drug by exploring novel delivery systems like nanoformulations or through the development of raloxifene analogs. Raloxifene has been effectively encapsulated in nanoparticles, such as styrene–maleic acid (SMA) micelles, which demonstrated superior pharmacokinetic profile than the free drug [95, 133].

As discussed in Table 4.2, Progesterone and GnRH receptors can be directly targeted by means of agonists, antagonists, or partial agonists and antagonists. Extensive research is in progress for finding numerous other potential approaches for targeting these receptor for the treatment of malignancies related to organs of reproductive system.

6 Receptor-Targeted Ligands in Clinical Development: Preclinical and Clinical Studies

6.1 Preclinical Studies

Table 4.3 describes the preclinical studies for drugs targeted to the receptors predominantly expressed in cancers of the reproductive system.

6.2 Clinical Trials

Table 4.4 gives an overview of the clinical trials that have been conducted to target the receptors relevant to the cancers of the reproductive system.

Table 4.3 Preclinical studies conducted to target the drugs to the receptors relevant to the cancers of the reproductive system

Sr. No.	Drug category	Name of the drug	Type of cancer in study	In vitro model	In vivo model	Endpoints/outcomes of study	References
1	Androgen antagonist	ONC1-13B	Prostate cancer	LnCAP cell line	CB17-SCID mice	Reduction in the expression of PSA and Ki67	[134]
2	Progesterone antagonist	Mifepristone in combination with cisplatin	Cervical cancer	CaSki and HeLa cell lines	Human xenografts of cervical tumors	Antiproliferative effect, Synergistic effect with cisplatin	[135]
3	Antiprogestin + Antiestrogen + Cytotoxic agent + Radiation therapy	Mifepristone + ICI 182, 783 + Cisplatin + Radiation therapy	Cervical cancer	HeLa cell line	Cervical xenografts	Cytotoxic effect of combination therapy	[136]
4	Estrogen antagonist	Fulvestrant	High-grade serous ovarian cancer (HGSOC)	HGCOC cells (2D, 3D and forced suspension culture)	Patient-derived xenografts	Blockade of ER-α expression, effect of 3D culture, and ER-α on cellular proliferation	[137]
5	LHRH agonist conjugated with cytotoxic agent	Zoptarelin doxorubicin (AN-152)	Prostate cancer	–	Mice xenografted with androgen-sensitive (LNCaP and MDA-Pca-2b) and androgen-independent (C4-2) cells	Antiproliferative effect	[138]

Table 4.4 Overview of the clinical trials conducted for drugs developed to target receptors relevant to the cancers of the reproductive system

Sr. No.	Drug/Drug combination	Mechanism of action	Phase	Age	Conditions	Dosage	Organization/ sponsor	Trial sites and year	Clinical trial identifier	Ref
Ovarian Cancer										
1	Ribociclib + Letrozole	A) CDK4/6 inhibitor B) Aromatase inhibitor	II	≥18 years	Estrogen receptor positive, postmenopausal and recurrent fallopian tube carcinomas; recurrent ovarian carcinoma;recurrent primary peritoneal carcinoma; recurrent uterine corpus carcinoma	NA	Mayo Clinic and National Cancer Institute (NCI)	United States, (2016–21)	NCT02657928	[139, 140]
2	Onapristone	Antiprogestin	I and II	≥18 years	Progesterone receptor positive tumor	Stage 1 (36 patients): Six dose cohorts, 5 using the ER formulation (10–50 mg BID) and 1 using the IR tablet formulation 100 mg RP2D: 50 mg Stage 2A: 10 patients with RP2D dose Stage 2B: 19 patients, dosing as per response obtained from Stage 2A	Arno Therapeutics	France (2014–16)	NCT02052128	[141]

3	Enzalutamide	Antiandrogen	II	≥18 years	Advanced epithelial ovarian, recurrent epithelial ovarian, fallopian tube, and primary peritoneal carcinoma	NA	Memorial Sloan Kettering Cancer Center and Medivation, Inc.	United States (2013–19)	NCT01974765	[142]
Cervical Cancer										
1	Tamoxifen and Letrozole	Adjuvant therapy of SERM and aromatase inhibitor	II	30–85	Uterine cervical neoplasm, squamous carcinoma of cervix	Phase 2: open-labeled, randomized trial of Tamoxifen (20 mg/day) and Letrozole (2.5 mg) with 44 patients followed 3 monthly for 12 months.	China Medical University Hospital, National Cheng-Kung University Hospital, Taiwan Ministry of Science and Technology, among others	Taiwan (2015–17)	NCT02482740	[143]
2	Metformin hydrochloride and Doxycycline	Blocking enzymes essential for cell growth	II	≥18 years	Breast carcinoma, Endometrial, clear cell adenocarcinoma, endometrial, serous adenocarcinoma, uterine corpus cancer, uterine corpus carcinosarcoma	Metformin hydrochloride, oral, daily, on days 1–3 and BID starting from day 4. Doxycycline oral, every 12 h, starting on day 1. Treatment was repeated for 7 days	Sidney Kimmel Cancer Center at Thomas Jefferson University	United States, Pennsylvania (2016–18)	NCT02874430	[144]

(continued)

Table 4.4 (continued)

Sr. No.	Drug/Drug combination	Mechanism of action	Phase	Age	Conditions	Dosage	Organization/ sponsor	Trial sites and year	Clinical trial identifier	Ref
Prostate Cancer										
1	Enzalu-tamide	Androgen receptor inhibitor	II	≥18 years	Localized prostate cancer	NA	The Netherlands Cancer Institute and Astellas Pharma Inc.	Details not available (2014–17)	NCT03297385	[145]
4	Niraparib + Abiraterone acetate and Prednisone	Niraparib: inhibition of PARP (Poly ADP ribose polymerase) enzyme and Abiraterone: Antiandrogen	I	≥18 years	Prostatic neoplasia, mCRPC	Open trial with dosage as follows: Niraparib – 200 mg/daily Abiraterone acetate – 1000 mg/daily Prednisone – 20 mg/daily	Janssen Research & Development, LLC	United states (2016–18)	NCT02924766	[146]

7 Conclusion and Critical Comments

Carcinogenesis in the different organs of the reproductive system, particularly, prostate, ovarian, and cervical tissues, involves aberrant expression of various physiological receptors belonging to different superfamilies. Structural and pharmacological role of four predominant receptors, namely, AR, ER, PR (sex steroid nuclear receptors), and GnRHR (GPCRs) has been highlighted in this chapter. Moreover, strategies and molecules developed for targeting these receptors, for formulating clinically relevant anticancer therapeutics, have been put forth and supported by the ongoing preclinical and clinical studies. We speculate that a combinatorial therapy comprising receptor-targeted ligands/agents, with clinically acceptable cytotoxic drugs, as well as targeting moieties such as antibodies (antibody–drug conjugates) and use of nano- and novel carriers for drug delivery, will enhance the overall antineoplastic effect. Considerable research has been conducted in deciphering the role of the AR and GnRHR in the cancers of the reproductive system and efforts to target these receptors have been commenced. We anticipate similar investigations to be conducted for ER and PR receptors in the near future.

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