

REVIEW

The androgen receptor amino-terminal domain: structure, function and therapeutic potential

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Abstract

Signalling by the steroid hormone testosterone involves the androgen receptor (AR), a structurally dynamic protein. The amino-terminal domain of the AR makes up more than half of the protein and has been found to be intrinsically disordered. This structural plasticity mediates receptor-dependent transcription, intradomain interactions and allosteric regulation. AR activity is a primary drug target in advanced and metastatic prostate cancer, a leading cause of cancer-related death in men. Recent research has focused on the amino-terminal domain as a novel drug target. In this review, we discuss the structural properties of the receptor and highlight some promising preclinical and clinical studies that aim to develop a drug discovery pipeline of small-molecule inhibitors targeting the amino-terminal domain.

Keywords: androgen receptor; prostate; endocrine therapy resistance

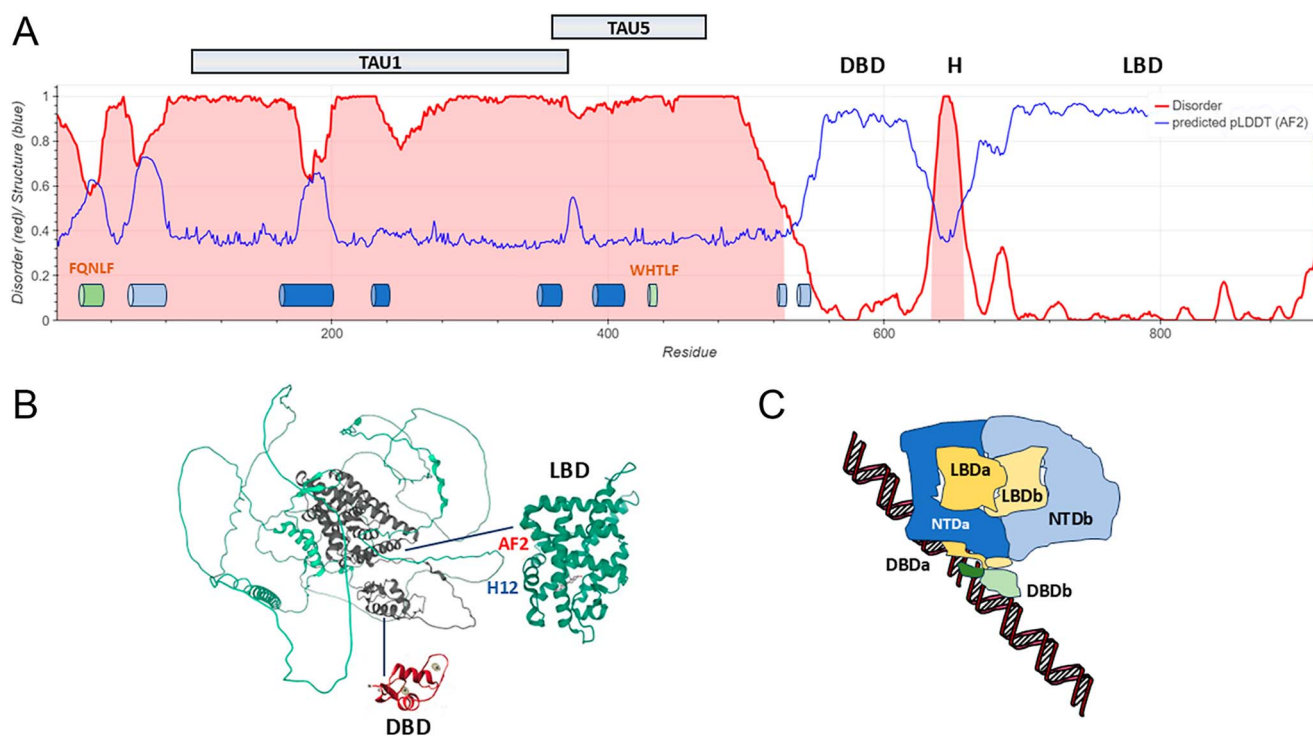
Introduction

The androgenic steroid hormone testosterone is produced by the Leydig cells of the testis and the theca cells of the ovary from cholesterol. Testosterone can be converted to the more potent androgen dihydrotestosterone (DHT) or the oestrogen oestradiol (E2) by the enzymes SRD5A and CPY19A1, respectively (McEwan & Brinkmann 2021). Androgens are important for male development, reproductive health and anabolic actions in non-reproductive tissues. The actions of testosterone and DHT are mediated primarily through the androgen receptor (AR), a member of the nuclear receptor superfamily (McEwan & Brinkmann 2021). The AR gene is located on the X chromosome and codes for a protein of 110 kDa and notably in tissues such as prostate and breast, the receptor mRNA is downregulated by androgens due to transcriptional repression (McEwan & Brinkmann 2021). In contrast, the binding of testosterone or DHT can lead to stabilisation of the receptor protein.

The AR protein has the typical domain organisation of the nuclear receptor superfamily, which includes

a ligand-binding domain (LBD) linked to a DNA-binding domain (DBD) by a short, flexible region at the C-terminal half of the protein (Fig. 1A). The remainder of the protein is made up of the amino-terminal domain (NTD) containing sequences critical for transcriptional regulation (McEwan & Brinkmann 2021). The AR-LBD and DBD have stable globular conformations rich in α -helices (He *et al.* 2004, Shaffer *et al.* 2004, Nadal *et al.* 2017) (Fig. 1B). In addition, the binding of testosterone causes helix 12 of the LBD to reposition, creating a surface pocket for protein–protein interactions, termed AF-2 (He *et al.* 2004) (Fig. 1B). In contrast to other steroid receptors, the AR-AF2 pocket has a strong preference for bulky hydrophobic residues and interacts with the FxxLF motif in the AR-NTD (Dubbink *et al.* 2004, He *et al.* 2004, Estébanez-Perpiñá *et al.* 2007). This interaction of the N- and C-termini influences hormone binding and target gene expression.

Disruption of androgen biosynthesis and/or mutations in the receptor have been correlated with disorders of sex development, hormone-dependent cancers,

**Figure 1**

Structural properties of the androgen receptor. (A) MolPhase prediction of intrinsically disordered and structural regions of the human AR, based on the primary amino acid sequence. Receptor domains are indicated above the prediction plots: the amino-terminal transactivation functions (TAU1 and TAU5) and the DBD, hinge (H) and LBD. Regions of α -helix structure (cylinders and the FqnLF and WhtLF motifs) in the amino-terminal domain are highlighted. (B) Structural prediction for the AR by α -fold. This shows the globular structural regions of the DBD and LBD and the intrinsically disordered nature of the NTD. The 3D-structures of the isolated DBD and LBD are shown for comparison: AF2, activation function 2 and the positioning of helix 12 are highlighted. (C) Schematic representation of the cryo-EM structure for the AR dimer bound to a DNA response element at ~ 13 Å (Yu *et al.* 2020).

polycystic ovarian syndrome disorder and Kennedy's disease, a neuromuscular disorder (McEwan & Brinkmann 2021). Therefore, it is unsurprising that investigating androgen signalling is a topic of interest for fundamental and clinical researchers as well as the pharmaceutical industry. In this review, we discuss some of the recent advances in our understanding of AR structure and its conformational dynamics, as well as the emergence of novel non-competitive inhibitors of AR function by targeting the AR-NTD.

AR-NTD

Early studies identified sequences within the AR-NTD that are essential for transactivation (TAU1 and TAU5), referred to as AF1 (Fig. 1A) (Simental *et al.* 1991, Jenster *et al.* 1995, Christiaens *et al.* 2002). Subsequent analyses identified binding sites for the transcription factor TFIIF (McEwan & Gustafsson 1997, De Mol *et al.* 2018), p160 coactivators (SRC1, 2 and 3) (Bevan *et al.* 1999, Reid *et al.* 2002b), co-chaperone proteins (Cato *et al.* 2017) and components of histone-modifying complexes (Zhu *et al.* 2006, Asangani *et al.* 2014). Thus, deletion of

the AR-NTD leads to a transcriptionally impaired protein, while loss of the AR-LBD produces a constitutively active transcription factor (see also below).

Structure

In contrast to the LBD and DBD, the AR-NTD has been shown to be structurally plastic and characterised by an intrinsically disordered structure (IDS). This was first demonstrated more than 20 years ago, and subsequent structural predictions, molecular dynamic modelling and experimental evidence have confirmed the intrinsically disordered nature of this domain (Reid *et al.* 2002a, Lavery & McEwan 2008, De Mol *et al.* 2016, Sheikhhassani *et al.* 2022). Secondary structure predictions, together with biochemical analysis and recent nuclear magnetic resonance (NMR) studies, have identified regions of α -helical propensity in the intrinsically disordered AR-NTD (Fig. 1A). Based on the primary amino acid sequence, a number of algorithms, for example, Ponder (Dunker *et al.* 2001), Metapredict (Emenecker *et al.* 2021) and MolPhase (Liang *et al.* 2024), have predicted IDS in the AR-NTD and hinge region linking the DBD and LBD (Fig. 1A).

Interestingly, these prediction plots also highlight some potential structured regions within the amino terminus that correspond, or are closely associated with, regions having the probability to form α -helix secondary structure (Fig. 1A). The results of NMR studies using a sub-region of AF1 (AF1*), which lacks the poly-glycine repeat and C-terminal amino acids, confirmed the IDS and identified the location of the predicted helical regions in TAU1 and TAU5 (Fig. 1A) (De Mol *et al.* 2016). NMR has also been used to characterise the regions of the NTD adjacent to the DBD, amino acids 518–555, identifying two segments of α -helical secondary structure (Fig. 1A) (Meyer *et al.* 2016). This region has been implicated in allosteric regulation of DNA binding (Liu *et al.* 2003).

A poly-glutamine repeat located near the C-terminus of the AR-NTD was found to cause Kennedy's disease, or spinal bulbar muscular atrophy, when the repeat expands above 38 residues, whereas the normal range is 5–36 residue repeats (Spada *et al.* 1991). This region has been found to be α -helical by circular dichroism (Davies *et al.* 2008) and NMR (Eftekharzadeh *et al.* 2016) spectroscopy, with the latter study also highlighting the importance of a leucine-rich sequence preceding the repeat for the helical conformation. Increasing the repeat length to 55 residues, found in an individual with Kennedy's disease, increased the propensity of the AR-NTD to form helical structure (Davies *et al.* 2008).

The conformational dynamics of the full-length AR-NTD has recently been investigated using molecular dynamic simulations and circuit topology (Sheikhhassani *et al.* 2022). This approach identified two distinct structural regions: an N-terminal region (NR), between amino acids 1 and 224, and a C-terminal region (CR), amino acids 225–538. The CR region was found to have more intramolecular contacts that were stable, and the cleft between the NR and CR could be modelled binding to the LBD (Sheikhhassani *et al.* 2022). Collectively, the above studies highlight the structural flexibility of the AR-NTD, the propensity to adopt α -helical secondary structure and suggest a model for allosteric regulation. However, a limitation of these studies is reliance on fragments of the AR-NTD in the absence of the DBD and LBD. Interestingly, α -fold (Varadi *et al.* 2024) fails to predict stable tertiary structure in the AR-NTD but does suggest regions of α -helix (Fig. 1B).

The first multidomain cryo-electron microscopy (EM) structure of the full-length AR complex has recently been reported by O'Malley and co-workers (Yu *et al.* 2020). This provides, for the first time, a three-dimensional model of the full-length receptor bound to DNA in a transcriptionally competent state and complexed with the key coregulatory binding partners SRC-3 and p300 (Yu *et al.* 2020) (Fig. 1C). The structure obtained revealed that the AR-NTD of each monomer creates a loop hugging the LBD domains, confirming the N/C interaction and dimerisation interfaces and highlighting key interacting surfaces with SRC-3 and

p300/CBP. The structure also suggested a stoichiometry of one molecule of SRC-3 and p300 per receptor dimer: SRC-3 interacted with the NTD of one monomer, while p300 bound to each of the NTDs in the dimer (Yu *et al.* 2020). Interestingly, the overall conformational arrangement of receptor domains and co-regulatory proteins revealed key distinctions from the oestrogen receptor (ER) and progesterone receptor (PR) complexes solved by the same research team (Yi *et al.* 2017, Yu *et al.* 2022). In the case of the ER α dimer, the NTDs flank the LBD and cooperate with this domain in the recruitment of two molecules of SRC-3 and the subsequent binding of p300 to SRC-3 (Yi *et al.* 2017). A similar orientation of the NTD flanking the LBD and DBD was observed for the PR dimer, creating surfaces for the binding of one molecule of SRC-2 with one receptor monomer and multiple contacts of p300 with the LBD and NTD of the second monomer (Yu *et al.* 2022). The structural model of the AR, together with biochemical and biophysical studies and recent dynamic modelling of the full-length NTD, presents a compelling picture for the role of the IDS in underpinning folding and allosteric dynamics and the generation of surfaces for co-regulatory protein interactions and assembly of a transcriptionally competent complex on DNA. As described above, the cryo-EM structure illustrated a binding stoichiometry of one molecule each of SRC-3 and p300 to the AR dimer bound to DNA (Yu *et al.* 2020), while NMR studies revealed the interaction between the WhlLF motif (TAU5) and the large subunit of TFIIF (RAP74-CTD) (De Mol *et al.* 2018). These studies are consistent with a model whereby induced folding of the AR-NTD creates a platform for the assembly of a transcriptionally competent complex.

Collectively, the findings from structural predictions, biophysical analysis, computational modelling and cryo-EM highlight the dynamic conformation of the AR-NTD, the presence of limited secondary structure and the propensity to form helical structure in the presence of chemical chaperone molecules and protein–protein interactions.

In addition to facilitating multiple protein–protein interactions, the IDS of the AR-NTD has also been shown to support allosteric regulation and, more recently, the formation of liquid–liquid phase separation (LLPS) condensates. Condensates, sometimes described as membrane-less organelles, can be comprised of proteins and nucleic acids and underpin numerous cellular processes, including transcriptional regulation (Hnisz *et al.* 2017). The formation of puncta in target cells by the AR has been known for some time (see van Royen *et al.* (2007)). However, there has been renewed interest in LLPS as a mechanism for assembling transcriptionally active complexes and, intriguingly, mediating resistance to antiandrogen drugs in prostate cancer (Xie *et al.* 2022). There is robust evidence for the importance of the IDS in condensate formation; however, it does not appear to be sufficient on its own, as

the isolated AR-NTD polypeptide fails to form LLPS (Ahmed *et al.* 2021, Xie *et al.* 2022, Zhang *et al.* 2023b); although, others have characterised the formation of droplets by the AR-NTD or splice variants lacking the LBD (Bouchard *et al.* 2018, Bielskutė *et al.* 2021, Roggero *et al.* 2022, Basu *et al.* 2023). In contrast, the structured AR-DBD appears to form condensates with RNA (Ahmed *et al.* 2021). The observed differences may reflect the experimental approaches used, for example, *in vitro* studies with purified receptor polypeptides compared with in-cell experiments using full-length AR or splice variants. Furthermore, the potential involvement of post-translational modifications and the concentration of receptor proteins may also influence the nature of the condensates formed and the role of different AR domains in LLPS. This is an area of increasing research focus and is likely to reveal new insights into the function of the AR-NTD.

Prostate cancer and the AR

Prostate cancer is the second most common cancer in men globally, and with ageing as a primary risk factor, together with environmental and genetic considerations, the incidence is expected to double over the next 15–20 years (Bray *et al.* 2018). Depending on the disease stage at diagnosis, treatment options include surgery (prostatectomy), radiotherapy or brachytherapy. For over 80 years, following the initial work by Huggins and Hodges in 1941, the standard treatment approach for advanced and metastatic disease is inhibiting the AR axis. This can involve reducing circulating testosterone levels (androgen ablation therapy) with or without the use of antiandrogens such as enzalutamide or more recent drugs, apalutamide and darolutamide (Fig. 2A) (reviewed in Estébanez-Perpiñá *et al.* (2021)). However, although initially highly effective at reducing prostate specific antigen (PSA) levels and tumour burden, the emergence of therapy resistance after 18–24 months blunts the efficacy of these androgen-targeted therapies. Further treatment can include switching to a different antiandrogen and/or combination with the CYP17A1 inhibitor abiraterone. However, therapy resistance leading to castrate-resistant prostate cancer (CRPC) occurs in up to 20% of patients. Resistance can arise through point mutations in the receptor ligand-binding pocket, the appearance of splice variants completely lacking the LBD and overexpression of the receptor protein (Fig. 2B) (Dehm *et al.* 2008, Hay & McEwan 2012, Tan *et al.* 2015). Mutation of residues involved in hydrogen bonding with the ligand (e.g. T878A) or forming the ligand-binding pocket (e.g. F876L) switches the antagonists bicalutamide and enzalutamide to agonists (reviewed in Tan *et al.* (2015)). The absence of the LBD through alternative splicing results in constitutively active forms of the AR (Dehm *et al.* 2008) (Fig. 2B). In addition to genetic changes,

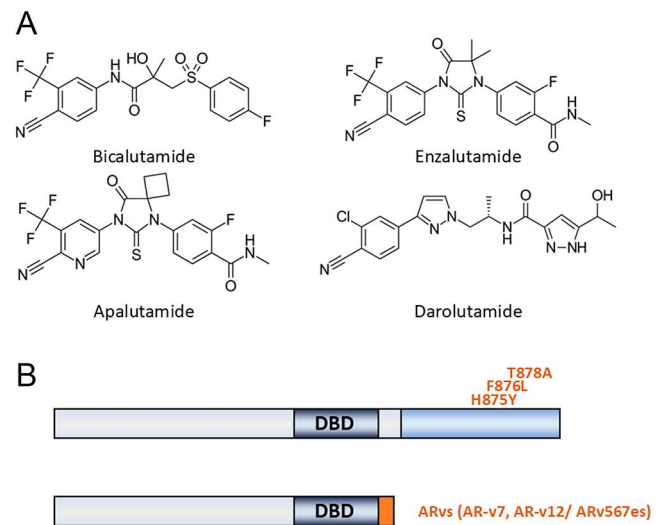


Figure 2

Anti-androgen drugs and receptor mutations. (A) Chemical structures of non-steroidal antiandrogens approved for hormone-sensitive or insensitive metastatic prostate cancer. (B) Schematic showing the domain structure of the AR and the location of point mutations in the LBD that lead to resistance to bicalutamide and enzalutamide. The lower diagram shows examples of splice variants (AR-v7 and AR-v12/ARv567es) lacking the LBD, which are functionally blind to current antiandrogen drugs.

overexpression of the AR protein is also known to impact antiandrogen effectiveness and lead to resistance (reviewed in Tan *et al.* (2015)). Crucially, the AR remains functionally important for tumorigenesis and metastasis (Chen *et al.* 2004). The lack of receptor-targeted therapies for resistant disease is therefore a clear unmet clinical need and an area of increasing research interest.

AR-NTD as a novel drug target

Covalent inhibitors of the AR-NTD

The intrinsically disordered nature of the AR-NTD makes it a challenging drug target. However, in a paradigm-shifting study, Sadar and co-workers identified a small molecule, EPI-001, which bound to the AR-NTD covalently and selectively disrupted protein–protein interactions, transcriptional regulation and, importantly, reduced tumour burden in xenograft models of prostate cancer (Andersen *et al.* 2010, Myung *et al.* 2013).

EPI-001 (Table 1) was originally isolated from a marine sponge and, together with the stereoisomer EPI-002 (2R, 20S) (Fig. 3A), demonstrated potency against both full-length AR and the AR-NTD fused to the GAL4 DNA-binding domain (Andersen *et al.* 2010, Myung *et al.* 2013). EPI-001 represents a bisphenol A diglycidyl ether (BADGE), and the presence of a chlorine was found to be essential for antiandrogen activity (Fig. 3), with binding to the AR-AF1 region demonstrated by steady-state fluorescence quenching (Andersen *et al.* 2010). Furthermore, EPI-001

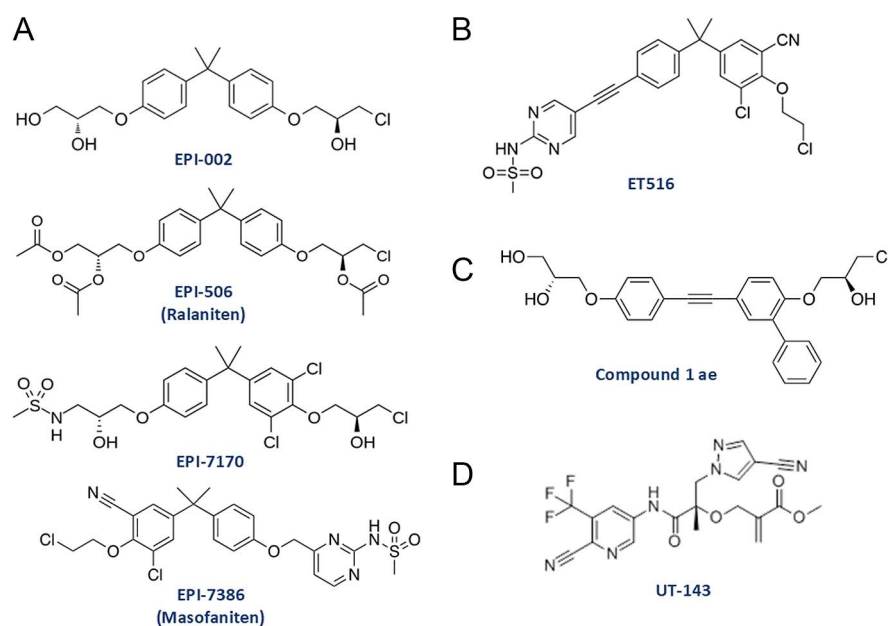
Table 1 Properties of a selection of AR-NTD inhibitors.

Compound	IC ₅₀		Selected pharmacokinetic properties	References
	Transactivation	Cell viability		
Enzalutamide	0.34 μM	-	-	Henry <i>et al.</i> (2023)
EPI-001	12.63 μM	ca 10 μM	T _{1/2} = 3.3 h (iv) F% = 86 [‡]	Myung <i>et al.</i> (2013)
EPI-7170	2.31 μM	2.7 μM	-	Hirayama <i>et al.</i> (2020)
ET516	0.2–0.7 μM	-	-	Xie <i>et al.</i> (2022)
1ae	1.54/4.1 μM*	1 μM	-	Basu <i>et al.</i> (2023)
UT-143	0.15 μM	-	T _{1/2} > 12 h (iv) Orally bioavailable	Thiyagarajan <i>et al.</i> (2023)
Compound 16	0.12 μM	-	T _{1/2} = 0.29 h (iv) F% = 16	Henry <i>et al.</i> (2023)
SC428	0.42/1.31 μM [†]	1.0–1.4 μM	-	Yi <i>et al.</i> (2023)
UT-34	0.2 μM	<2 μM	T _{1/2} = 1.3 h (<i>in vitro</i> MLM [§]) Orally bioavailable	Ponnusamy <i>et al.</i> (2019), He <i>et al.</i> (2021)
Compound 26f	0.38 μM	-	T _{1/2} = 4.42 h (<i>in vitro</i> MLM [§]) Orally bioavailable	He <i>et al.</i> (2021)
Z15	0.22 μM	1.37–3.63 μM	-	Wu <i>et al.</i> (2023)
Compound 27c	-	0.9 μM	T _{1/2} = 1.4 h (iv) F% = 18	Xiao <i>et al.</i> (2024)
BWA-522	-	1.07–5.59 μM	T _{1/2} = 3.12 h (<i>in vitro</i> MLM [§]) Orally bioavailable	Zhang <i>et al.</i> (2023a)

*AR-v7. †ARv7/ARv567es. ‡F% = oral bioavailability. §MLM = mouse liver microsomes.

selectively inhibited protein–protein interactions, including TFIIF and CBP/p300, with the AR transactivation domain (Andersen *et al.* 2010, Myung *et al.* 2013). The WthLF motif, present in TAU5 (Fig. 1A), is critical for ligand-independent activity of the AR, and binding of EPI-001/2 has been mapped to sequences in TAU5 experimentally by NMR (De Mol *et al.* 2016) and, more recently, by molecular dynamic modelling of the full-length AR-NTD (Sheikhhassani *et al.* 2022). Subsequent analysis by Zhu *et al.* (2022) has calculated binding affinities for EPI-002 and the next-generation analogue EPI-7170 (Fig. 3A) in the μM range ($K_D = 5.4$ and 1.9 μM, respectively) with a TAU5 fragment, representing the previously identified helical regions (amino acids 391–446). In addition, the binding of EPI-002 and EPI-7170, increased the propensity for α-helical secondary structure in molecular dynamic simulations, suggesting a more folded, compact conformation for this TAU5 polypeptide (Zhu *et al.* 2022).

EPI-001, the stereoisomer EPI-002, the pro-drug EPI-506, and the next-generation analogue EPI-7170 (Fig. 3A) have all demonstrated efficacy in *in vivo* models using prostate cancer cell xenografts (LNCaP, LNCaP95 and VCaP). EPI compounds reduced tumour burden and markers of cell proliferation and increased markers of apoptosis (Andersen *et al.* 2010, Myung *et al.* 2013, Banuelos *et al.* 2020, Hirayama *et al.* 2020) (Table 1). There have also been promising results in preclinical studies for combination therapies with enzalutamide (Hirayama *et al.* 2020), chemotherapy (docetaxel) (Martin *et al.* 2014) and radiotherapy (Banuelos *et al.* 2020). EPI-506, Ralaniten (Fig. 3A), was the first-in-man clinical trial (NCT02606123) for an AR-NTD inhibitor, and although the study was terminated, the compound was well tolerated. Ongoing clinical trials evaluating the latest iteration of this series, EPI-7386 (Masofaniten, Fig. 3A), as a monotherapy for metastatic CRPC (NCT04421222) and in combination with enzalutamide alone

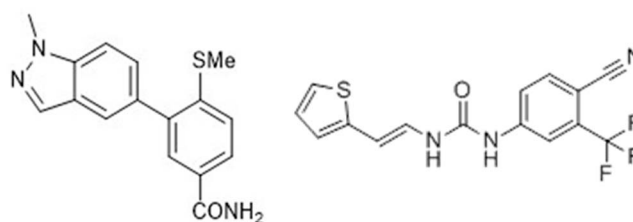
**Figure 3**

Examples of non-competitive covalent AR-NTD inhibitors. (A) Examples derived from EPI-001. (B, C, D) Examples that are chemically related (ET516) or distinct from EPI-001 (compound 1ae, UT-143). See text for details.

(NTC05075577) or together with androgen deprivation treatment (NCT06312670) for metastatic hormone-sensitive prostate cancer. Preliminary results for NTC05075577 phase I trial report no safety concerns, but a reduction in EPI-7386 levels due to enzalutamide induction of CYP3A4 was observed, which was compensated by a twice-daily dose of the drug (Laccetti *et al.* 2023). However, this trial has recently been stopped as primary outcomes were unlikely to be met.

Recently, using a novel LLPS phenotypic screen of a bespoke library of compounds based on the EPI-001 scaffold, Xie *et al.* (2022) identified ET516 (Fig. 3B, Table 1), sharing a number of the pharmacological features associated with this class of compound. ET516 effectively inhibited expression of an AR-target gene signature (e.g. KLK3/PSA, TMPRSS2, NKX3-1 and FKBP5), decreased cell viability in AR-positive cells and blocked growth *in vivo* of an LNCaP xenograft. Significantly, and in contrast to EPI-001, ET516 efficiently blocked the formation of nuclear puncta by hormone-activated AR in a concentration-dependent manner (Xie *et al.* 2022). Furthermore, puncta formed by AR-v7 were found to be resistant to enzalutamide treatment but sensitive to ET516, leading the authors to suggest that therapy resistance to conventional LBD-targeted antiandrogens could involve phase separation of the AR protein. Salvatella and co-workers, in a wide-ranging study, also investigated the properties of LLPS of the AR-FL and -v7 splice variant. This demonstrated the involvement of tyrosine residues and helical segments in condensate formation, and EPI-001 was found to partition with the AR-NTD in droplets (Basu *et al.* 2023). Using a rational chemical synthesis approach aimed at optimising the spacer connecting the aromatic rings found in EPI-001, as well as the associated substitution patterns, these authors identified a series of small molecules with increased potency and binding to the TAU5 region, for example, small molecules 1aa and 1ae (Fig. 3C, Table 1) (Basu *et al.* 2023).

Recently, UT-143 (Fig. 3D, Table 1) was identified from a library based on selective AR degraders (i.e. selective androgen receptor degrader (SARD) UT-34, Thiyagarajan *et al.* 2023) and represents another class of covalent inhibitors of the AR-NTD. UT-143 was selective for the AR and inhibited wild-type and mutant receptors associated with antiandrogen resistance (i.e. W741L, F876L and T878A) and the AR-v7 splice variant. Binding to AR-AF1 was demonstrated, and the cysteines at positions 327 and 406 were identified as targets for covalent binding using an embedded Michael acceptor as a reactive group. Similar to ET516, UT-143 disrupted condensate formation and inhibited both hormone-dependent and -independent growth *in vitro* as well as reducing tumour burden *in vivo* (Thiyagarajan *et al.* 2023). Taken together, the studies with ET516 and UT-143 highlight a novel mechanism of AR inhibition involving the disruption of LLPS condensates that can



Compound 16

SC428

Figure 4

Examples of non-competitive AR-NTD inhibitors.

overcome resistance to antiandrogens such as enzalutamide.

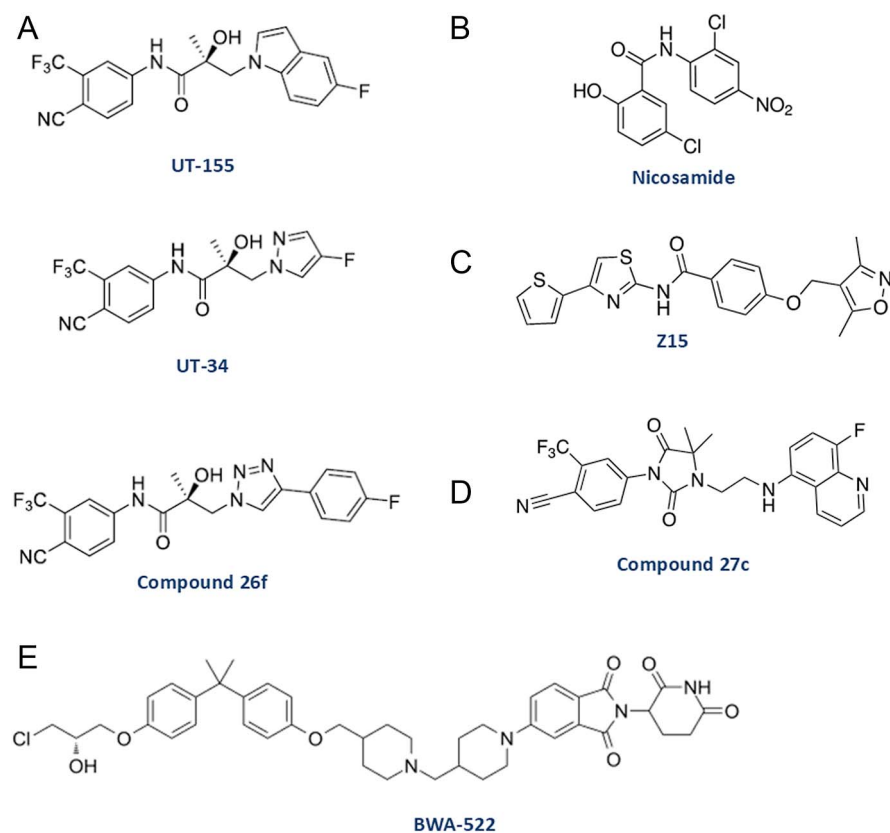
Non-competitive, reversible inhibitors of the AR-NTD

Examples of other chemotypes, structurally unique chemical templates, that have shown promise in targeting the AR-NTD, are compound 16 and SC428 (Fig. 4, Table 1). SC428 is a urea derivative and is therefore a different chemotype to compound 16, which is a biaryl system. Accordingly, these have distinct structural features that differentiate them from each other. SC428 demonstrated good potency against transcriptional activation by AR splice variants v7 and v567es, with IC_{50} values of 0.42 and 1.31 μ M, respectively, and an apparent dissociation constant for binding the AR-NTD, $K_D = 75 \mu$ M (Yi *et al.* 2023). SC428 also inhibited hormone-dependent nuclear translocation of the AR and cell proliferation of LNCaP (AR-FL and T878A mutation) and VCaP (AR-FL, AR-v7 and v567es) cells comparable to enzalutamide but was significantly more potent in the 22Rv1 (AR-FL, AR-v1, 3, 7 and 12) CRPC cell model both *in vitro* and *in vivo* in intact mice (Yi *et al.* 2023).

In our laboratories, we have explored a novel series of biaryl compounds following hit identification after a high-throughput screen using a pan-AR-v construct and a luciferase reporter gene cell line (Monaghan *et al.* 2022, Henry *et al.* 2023). Compound 16 (Fig. 4, Table 1) demonstrated excellent potency against AR-FL hormone-dependent transcriptional activity or an AR-v in the absence of hormone when tested in VCaP cells. Table 1 shows the associated potency of the compound alongside its pharmacokinetic profile, which, although it has measurable oral exposure, the associated half-life would require improvement before any related small molecule inhibitors from this series of compounds could be used for *in vivo* xenograft models.

AR degraders targeting the AR-NTD

An alternative approach to switching off AR signalling in prostate cancer involves compounds that target the

**Figure 5**

Examples of receptor degraders targeting the AR-NTD. (A) Compounds related to the UT SARDs. (B, C, D, E) Other SARDs include the anthelmintic nicosamide, Z15, compound 27c and BW-522.

receptor for degradation by the proteasomal apparatus, including proteolysis-targeting chimeras or PROTACs (for recent review see [Chen *et al.* \(2024\)](#)). Several AR degraders have shown promise in preclinical studies and have advanced into clinical trials, most notably UT-34 analogue (ONCT-345/GTx-534) (NCT05917470) and nicosamide (NCT02532114, NCT03123978 and NCT02807805) (see [Fig. 5, Table 1](#)). However, recently the trial evaluating ONCT-534 was stopped as significant clinical improvements were not observed (<https://investor.oncternal.com/news-releases/news-release-details/oncternal-therapeutics-announces-termination-its-clinical>, September 2024).

The UT series (UT-155, UT-34 and compound 26f, [Fig. 5A](#)) of SARDs were originally based on ligands with agonist (enobosarm) or antagonist (bicalutamide) activity. Intriguingly, however, UT-155 was found to bind to both the AR-LBD and -NTD and demonstrated target engagement with AR-vs, exhibiting an $IC_{50} = 0.078 \mu\text{M}$ for inhibition of transcriptional activity and degradation of the protein ([Ponnusamy *et al.* 2019](#)). Further chemical synthesis and modification led to UT-34 with improved *in vivo* activity and compound 26f with an improved pharmacokinetic profile ([Table 1](#)) ([He *et al.* 2021](#), [Narayanan 2021](#)).

Nicosamide ([Fig. 5B](#)) is an FDA-approved anthelmintic drug that has been repurposed and tested in several clinical trials ([Parikh *et al.* 2021](#)). It has been found to

cause degradation of the full-length and AR-v7 splice variant and was effective in cell model and xenograft studies ([Liu *et al.* 2014, 2016](#)). However, evidence for direct binding to the AR-NTD is more limited, raising questions about the precise mechanism of action. More recently, two novel SARDs have been identified: Z15 ([Fig. 5C, Table 1](#)) and compound 27c ([Fig. 5D, Table 1](#)) ([Wu *et al.* 2023](#), [Xiao *et al.* 2024](#)). These compounds demonstrated good potency in inhibiting receptor-dependent transactivation and/or in prostate cell proliferation ([Table 1](#)). Z15 was found to be a dual inhibitor, interacting with both the LBD and NTD ([Wu *et al.* 2023](#)). The starting scaffold for compound 27c was the aryl-hydantoin moiety found in enzalutamide and an 'N-heterocycle degron', which, after systematic structure-function studies, resulted in a panel of monovalent degraders ([Xiao *et al.* 2024](#)). Compound 27c demonstrated inhibition of AR target genes, binding to AR-NTD (determined by surface plasmon resonance) and loss of cell viability ([Xiao *et al.* 2024](#)).

BWA-522 is a promising PROTAC targeting the AR-NTD, which links the EPI-001 skeleton to an E3-ligase ligand cereblon (CRBN) ([Fig. 5E; Zhang *et al.* 2023a](#)). BWA-522 caused degradation of the full-length AR and AR-v7 and loss of cell viability in a range of prostate cancer cell models. Furthermore, BW-522 showed promising pharmacokinetic properties ([Table 1](#)) and inhibited tumour growth *in vivo* ([Zhang *et al.* 2023a](#)).

In this section, we have given a brief overview of AR-NTD inhibitors, focusing on those in clinical trial, that have demonstrated binding to the NTD and/or compounds altering the structural properties of this domain. For a recent authoritative review of non-competitive inhibitors of the AR, see [Riley *et al.* \(2023\)](#).

Conclusions and future perspectives

Since the isolation of the first AR cDNA over 30 years ago, there have been significant advances in our understanding of AR protein structure and function and the mechanisms regulating expression in different tissues. Central to this has been the insight gained from understanding the properties of the intrinsically disordered NTD. The structural plasticity of this domain underpins receptor-protein interactions and allosteric regulation. Coupling folding with function facilitates specific interactions in the absence of high-affinity binding and creates large surface areas for protein-protein interactions. In recent years, the AR-NTD has also become a major focus for drug screening programmes as novel targets for switching off receptor activity are explored to treat therapy-resistant prostate cancer.

However, several key research questions remain, including the role of the AR-NTD and/or other receptor domains in LLPS condensate formation. Recent findings link the formation of condensates with mutant receptors and resistance to traditional AR inhibitors. Defining the composition and nature of these condensates will be important to our understanding of receptor signalling in both normal and disease conditions.

Evidence from *in vitro* and computational studies clearly supports the IDS in the AR and the propensity of regions of the NTD to adopt an α -helical structure. However, in the context of the cellular environment, what constraints are there on this structural flexibility and is this linked to intracellular location and/or binding partners? Does receptor dimerization and DNA binding favour the ‘hugging’ model seen in the cryo-EM structures, or is this one of many likely conformations adopted by the NTD? Exciting developments in methods such as in-cell NMR spectroscopy ([Kang 2019](#)) may shed some light on this question.

Importantly, can the promising preclinical developments in identifying small molecule inhibitors of the AR-NTD be translated into new drugs for the treatment of men with advanced prostate cancer? With the incidence of prostate cancer predicted to double in the next 20 years and the continued emergence of resistance to conventional AR-LBD inhibitors, the goal is to develop new therapies. It is to be hoped, indeed expected, that increased understanding of the molecular and structural properties of the AR will realise this goal in the next 5–10 years.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the work.

Funding

This work did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Acknowledgements

Work in the authors’ groups on targeting the AR-NTD has been supported by funding from MRC DPFS award (MR/T02559X/1) and Prostate Cancer Research (grant 6956).

References

- Ahmed J, Meszaros A, Lazar T, *et al.* 2021 DNA-binding domain as the minimal region driving RNA-dependent liquid-liquid phase separation of androgen receptor. *Protein Sci* **30** 1380–1392. (<https://doi.org/10.1002/pro.4100>)
- Andersen RJ, Mawji NR, Wang J, *et al.* 2010 Regression of castrate-recurrent prostate cancer by a small-molecule inhibitor of the amino-terminus domain of the androgen receptor. *Cancer Cell* **17** 535–546. (<https://doi.org/10.1016/j.ccr.2010.04.027>)
- Asangani IA, Dommeti VL, Wang X, *et al.* 2014 Therapeutic targeting of BET bromodomain proteins in castration-resistant prostate cancer. *Nature* **510** 278–282. (<https://doi.org/10.1038/nature13229>)
- Banuelos CA, Ito Y, Obst JK, *et al.* 2020 Ralaniten sensitizes enzalutamide-resistant prostate cancer to ionizing radiation in prostate cancer cells that express androgen receptor splice variants. *Cancers* **12** 1991. (<https://doi.org/10.3390/cancers12071991>)
- Basu S, Martínez-Cristóbal P, Frigolé-Vivas M, *et al.* 2023 Rational optimization of a transcription factor activation domain inhibitor. *Nat Struct Mol Biol* **30** 1958–1969. (<https://doi.org/10.1038/s41594-023-01159-5>)
- Bevan CL, Hoare S, Claessens F, *et al.* 1999 The AF1 and AF2 domains of the androgen receptor interact with distinct regions of SRC1. *Mol Cell Biol* **19** 8383–8392. (<https://doi.org/10.1128/mcb.19.12.8383>)
- Bielskute S, Garcia-Cabau C, Frigolé-Vivas M, *et al.* 2021 Low amounts of heavy water increase the phase separation propensity of a fragment of the androgen receptor activation domain. *Protein Sci* **30** 1427–1437. (<https://doi.org/10.1002/pro.4110>)
- Bouchard JJ, Otero JH, Scott DC, *et al.* 2018 Cancer mutations of the tumor suppressor SPOP disrupt the formation of active, phase-separated compartments. *Mol Cell* **72** 19–36.e8. (<https://doi.org/10.1016/j.molcel.2018.08.027>)
- Bray F, Ferlay J, Soerjomataram I, *et al.* 2018 Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* **68** 394–424. (<https://doi.org/10.3322/caac.21492>)
- Cato L, Neeb A, Sharp A, *et al.* 2017 Development of Bag-1L as a therapeutic target in androgen receptor-dependent prostate cancer. *Elife* **6** e27159. (<https://doi.org/10.7554/elife.27159>)
- Chen CD, Welsbie DS, Tran C, *et al.* 2004 Molecular determinants of resistance to antiandrogen therapy. *Nat Med* **10** 33–39. (<https://doi.org/10.1038/nm972>)
- Chen QH, Munoz E & Ashong D 2014 Insight into recent advances in degrading androgen receptor for castration-resistant prostate cancer. *Cancers* **16** 663. (<https://doi.org/10.3390/cancers16030663>)

- Christiaens V, Bevan CL, Callewaert L, *et al.* 2002 Characterization of the two coactivator-interacting surfaces of the androgen receptor and their relative role in transcriptional control. *J Biol Chem* **277** 49230–49237. (<https://doi.org/10.1074/jbc.m209322200>)
- Davies P, Watt K, Kelly S, *et al.* 2008 Consequences of poly-glutamine repeat length for the conformation and folding of the androgen receptor amino-terminal domain. *J Mol Endocrinol* **41** 301–314. (<https://doi.org/10.1677/jme-08-0042>)
- Dehm SM, Schmidt LJ, Heemers HV, *et al.* 2008 Splicing of a novel androgen receptor exon generates a constitutively active androgen receptor that mediates prostate cancer therapy resistance. *Cancer Res* **68** 5469–5477. (<https://doi.org/10.1158/0008-5472.can-08-0594>)
- De Mol E, Fenwick RB, Phang CT, *et al.* 2016 EPI-001, A compound active against castration-resistant prostate cancer, targets transactivation unit 5 of the androgen receptor. *ACS Chem Biol* **11** 2499–2505. (<https://doi.org/10.1021/acschembio.6b00182>)
- De Mol E, Szulc E, Di Sanza C, *et al.* 2018 Regulation of androgen receptor activity by transient interactions of its transactivation domain with general transcription regulators. *Structure* **26** 145–152.e3. (<https://doi.org/10.1016/j.str.2017.11.007>)
- Dubbink HJ, Hersmus R, Verma CS, *et al.* 2004 Distinct recognition modes of FXXLF and LXXLL motifs by the androgen receptor. *Mol Endocrinol* **18** 2132–2150. (<https://doi.org/10.1210/me.2003-0375>)
- Dunker AK, Lawson JD, Brown CJ, *et al.* 2001 Intrinsically disordered protein. *J Mol Graph Model* **19** 26–59. ([https://doi.org/10.1016/s1093-3263\(00\)00138-8](https://doi.org/10.1016/s1093-3263(00)00138-8))
- Emenecker RJ, Griffith D & Holehouse AS 2021 Metapredict: a fast, accurate, and easy-to-use predictor of consensus disorder and structure. *Biophys J* **120** 4312–4319. (<https://doi.org/10.1016/j.bpj.2021.08.039>)
- Eftekhazadeh B, Piai A, Chiesa G, *et al.* 2016 Sequence context influences the structure and aggregation behavior of a PolyQ tract. *Biophys J* **110** 2361–2366. (<https://doi.org/10.1016/j.bpj.2016.04.022>)
- Estébanez-Perpiñá E, Arnold LA, Nguyen P, *et al.* 2007 A surface on the androgen receptor that allosterically regulates coactivator binding. *Proc Natl Acad Sci U S A* **104** 16074–16079. (<https://doi.org/10.1073/pnas.0708036104>)
- Estébanez-Perpiñá E, Bevan CL & McEwan IJ 2021 Eighty years of targeting androgen receptor activity in prostate cancer: the fight goes on. *Cancers* **13** 509. (<https://doi.org/10.3390/cancers13030509>)
- Hay CW & McEwan IJ 2012 The impact of point mutations in the human androgen receptor: classification of mutations on the basis of transcriptional activity. *PLoS One* **7** e32514. (<https://doi.org/10.1371/journal.pone.0032514>)
- He B, Gampe RT Jr, Kole AJ, *et al.* 2004 Structural basis for androgen receptor interdomain and coactivator interactions suggests a transition in nuclear receptor activation function dominance. *Mol Cell* **16** 425–438. (<https://doi.org/10.1016/j.molcel.2004.09.036>)
- He Y, Hwang DJ, Ponnusamy S, *et al.* 2021 Exploration and biological evaluation of basic heteromonocyclic propanamide derivatives as SARDs for the treatment of enzalutamide-resistant prostate cancer. *J Med Chem* **64** 11045–11062. (<https://doi.org/10.1021/acs.jmedchem.1c00439>)
- Henry MC, Riley CM, Hunter I, *et al.* 2023 Synthesis and evaluation of small molecule inhibitors of the androgen receptor N-terminal domain. *ACS Med Chem Lett* **14** 1800–1806. (<https://doi.org/10.1021/acsmedchemlett.3c00426>)
- Hirayama Y, Tam T, Jian K, *et al.* 2020 Combination therapy with androgen receptor N-terminal domain antagonist EPI-7170 and enzalutamide yields synergistic activity in AR-V7-positive prostate cancer. *Mol Oncol* **14** 2455–2470. (<https://doi.org/10.1002/1878-0261.12770>)
- Hnisz D, Shrinivas K, Young RA, *et al.* 2017 A phase separation model for transcriptional control. *Cell* **169** 13–23. (<https://doi.org/10.1016/j.cell.2017.02.007>)
- Jenster G, van der Korput HA, Trapman J, *et al.* 1995 Identification of two transcription activation units in the N-terminal domain of the human androgen receptor. *J Biol Chem* **270** 7341–7346. (<https://doi.org/10.1074/jbc.270.13.7341>)
- Kang CB 2019 Applications of in-cell NMR in structural biology and drug discovery. *Int J Mol Sci* **20** 139. (<https://doi.org/10.3390/ijms20010139>)
- Laccetti AL, Chatta GS, Iannotti N, *et al.* 2023 Phase 1/2 study of EPI-7386 in combination with enzalutamide (enz) compared with enz alone in subjects with metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol* **41** (Supplement 179) 179. (https://doi.org/10.1200/JCO.2023.41.6_suppl.179)
- Lavery DN & McEwan IJ 2008 Structural characterization of the native NH2-terminal transactivation domain of the human androgen receptor: a collapsed disordered conformation underlies structural plasticity and protein-induced folding. *Biochemistry* **47** 3360–3369. (<https://doi.org/10.1021/bi702221e>)
- Liang Q, Peng N, Xie Y, *et al.* 2024 MolPhase, an advanced prediction algorithm for protein phase separation. *EMBO J* **43** 1898–1918. (<https://doi.org/10.1038/s44318-024-00090-9>)
- Liu C, Lou W, Zhu Y, *et al.* 2014 Niclosamide inhibits androgen receptor variants expression and overcomes enzalutamide resistance in castration-resistant prostate cancer. *Clin Cancer Res* **20** 3198–3210. (<https://doi.org/10.1158/1078-0432.CCR-13-3296>)
- Liu GZ, Wang H & Wang Z 2003 Identification of a highly conserved domain in the androgen receptor that suppresses the DNA-binding domain-DNA interactions. *J Biol Chem* **278** 14956–14960. (<https://doi.org/10.1074/jbc.m212229200>)
- Liu C, Armstrong C, Zhu Y, *et al.* 2016 Niclosamide enhances abiraterone treatment via inhibition of androgen receptor variants in castration resistant prostate cancer. *Oncotarget* **7** 32210–32220. (<https://doi.org/10.18632/oncotarget.8493>)
- Martin SK, Banuelos CA, Sadar MD, *et al.* 2014 N-terminal targeting of androgen receptor variant enhances response of castration resistant prostate cancer to taxane chemotherapy. *Mol Oncol* **9** 628–639. (<https://doi.org/10.1016/j.molonc.2014.10.014>)
- McEwan IJ & Brinkmann AO 2021 Androgen physiology: receptor and metabolic disorders. In *Endotext*. Eds KR Feingold, B AnaWalt & A Boyce. South Dartmouth, MA, USA: MDText.com, Inc. (<https://www.ncbi.nlm.nih.gov/books/NBK279028/>)
- McEwan IJ & Gustafsson J 1997 Interaction of the human androgen receptor transactivation function with the general transcription factor TFIIF. *Proc Natl Acad Sci U S A* **94** 8485–8490. (<https://doi.org/10.1073/pnas.94.16.8485>)
- Meyer S, Wang YH, Pérez-Escrivà P, *et al.* 2016 Backbone 1H, 15N, 13C NMR assignment of the 518–627 fragment of the androgen receptor encompassing N-terminal and DNA binding domains. *Biomol NMR Assign* **10** 175–178. (<https://doi.org/10.1007/s12104-015-9661-8>)
- Monaghan AE, Porter A, Hunter I, *et al.* 2022 Development of a high-throughput screening assay for small-molecule inhibitors of androgen receptor splice variants. *Assay Drug Dev Technol* **20** 111–124. (<https://doi.org/10.1089/adt.2021.128>)
- Myung JK, Banuelos CA, Fernandez JG, *et al.* 2013 An androgen receptor N-terminal domain antagonist for treating prostate cancer. *J Clin Invest* **123** 2948–2960. (<https://doi.org/10.1172/jci66398>)

- Nadal M, Prekovic S, Gallastegui N, *et al.* 2017 Structure of the homodimeric androgen receptor ligand-binding domain. *Nat Commun* **8** 14388. (<https://doi.org/10.1038/ncomms14388>)
- Narayanan R 2021 Androgen receptor (AR) abstract LBA016: androgen receptor (AR) N-Terminus-Domain-Binding small molecule degraders for the treatment of AR splice variant-positive castration-resistant prostate cancer. *Mol Cancer Therapeut* **20** (Supplement 12) LBA016. (<https://doi.org/10.1158/1535-7163.targ-21-lba016>)
- Parikh M, Liu C, Wu CY, *et al.* 2021 Phase Ib trial of reformulated niclosamide with abiraterone/prednisone in men with castration-resistant prostate cancer. *Sci Rep* **11** 6377. (<https://doi.org/10.1038/s41598-021-85969-x>)
- Ponnusamy S, He Y, Hwang DJ, *et al.* 2019 Orally bioavailable androgen receptor degrader, potential next-generation therapeutic for enzalutamide-resistant prostate cancer. *Clin Cancer Res* **25** 6764–6780. (<https://doi.org/10.1158/1078-0432.ccr-19-1458>)
- Reid J, Kelly SM, Watt K, *et al.* 2002a Conformational analysis of the androgen receptor amino-terminal domain involved in transactivation. Influence of structure-stabilizing solutes and protein-protein interactions. *J Biol Chem* **277** 20079–20086. (<https://doi.org/10.1074/jbc.m201003200>)
- Reid J, Murray I, Watt K, *et al.* 2002b The androgen receptor interacts with multiple regions of the large subunit of general transcription factor TFIIF. *J Biol Chem* **277** 41247–41253. (<https://doi.org/10.1074/jbc.m205220200>)
- Riley CM, Elwood JML, Henry MC, *et al.* 2023 Current and emerging approaches to noncompetitive AR inhibition. *Med Res Rev* **43** 1701–1747. (<https://doi.org/10.1002/med.21961>)
- Roggero CM, Esser V, Duan L, *et al.* 2022 Poly-glutamine-dependent self-association as a potential mechanism for regulation of androgen receptor activity. *PLoS One* **17** e0258876. (<https://doi.org/10.1371/journal.pone.0258876>)
- Simental JA, Sar M, Lane MV, *et al.* 1991 Transcriptional activation and nuclear targeting signals of the human androgen receptor. *J Biol Chem* **266** 510–518. ([https://doi.org/10.1016/s0021-9258\(18\)52466-2](https://doi.org/10.1016/s0021-9258(18)52466-2))
- Shaffer PL, Jivan A, Dollins DE, *et al.* 2004 Structural basis of androgen receptor binding to selective androgen response elements. *Proc Natl Acad Sci U S A* **101** 4758–4763. (<https://doi.org/10.1073/pnas.0401123101>)
- Sheikhassani V, Scalvini B, Ng J, *et al.* 2022 Topological dynamics of an intrinsically disordered N-terminal domain of the human androgen receptor. *Protein Sci* **31** e4334. (<https://doi.org/10.1002/pro.4334>)
- Spada ARL, Wilson EM, Lubahn DB, *et al.* 1991 Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy. *Nature* **352** 77–79. (<https://doi.org/10.1038/352077a0>)
- Tan MHE, Li J, Xu HE, *et al.* 2015 Androgen receptor: structure, role in prostate cancer and drug discovery. *Acta Pharmacol Sin* **36** 3–23. (<https://doi.org/10.1038/aps.2014.18>)
- Thiyagarajan T, Ponnusamy S, Hwang DJ, *et al.* 2023 Inhibiting androgen receptor splice variants with cysteine-selective irreversible covalent inhibitors to treat prostate cancer. *Proc Natl Acad Sci U S A* **120** e2211832120. (<https://doi.org/10.1073/pnas.2211832120>)
- van Royen ME, Cunha SM, Brink MC, *et al.* 2007 Compartmentalization of androgen receptor protein-protein interactions in living cells. *J Cell Biol* **177** 63–72. (<https://doi.org/10.1083/jcb.200609178>)
- Varadi M, Bertoni D, Magana P, *et al.* 2024 AlphaFold Protein Structure Database in 2024: providing structure coverage for over 214 million protein sequences. *Nucleic Acids Res* **52** D368–D375. (<https://doi.org/10.1093/nar/gkad1011>)
- Wu M, Zhang R, Zhang Z, *et al.* 2023 Selective androgen receptor degrader (SARD) to overcome antiandrogen resistance in castration-resistant prostate cancer. *Elife* **12** e70700. (<https://doi.org/10.7554/elife.70700>)
- Xiao M, Ha S, Zhu J, *et al.* 2024 Structure-activity relationship (SAR) studies of novel monovalent AR/AR-V7 dual degraders with potent efficacy against advanced prostate cancer. *J Med Chem* **67** 5567–5590. (<https://doi.org/10.1021/acs.jmedchem.3c02177>)
- Xie J, He H, Kong W, *et al.* 2022 Targeting androgen receptor phase separation to overcome antiandrogen resistance. *Nat Chem Biol* **18** 1341–1350. (<https://doi.org/10.1038/s41589-022-01151-y>)
- Yi P, Wang Z, Feng Q, *et al.* 2017 Structural and functional impacts of ER coactivator sequential recruitment. *Mol Cell* **67** 733–743.e4. (<https://doi.org/10.1016/j.molcel.2017.07.026>)
- Yi Q, Liu W, Seo JH, *et al.* 2023 Discovery of a small-molecule inhibitor targeting the androgen receptor N-terminal domain for castration-resistant prostate cancer. *Mol Cancer Ther* **22** 570–582. (<https://doi.org/10.1158/1535-7163.mct-22-0237>)
- Yu X, Yi P, Hamilton RA, *et al.* 2020 Structural insights of transcriptionally active, full-length androgen receptor coactivator complexes. *Mol Cell* **79** 812–823.e4. (<https://doi.org/10.1016/j.molcel.2020.06.031>)
- Yu X, Yi P, Panigrahi AK, *et al.* 2022 Spatial definition of the human progesterone receptor-B transcriptional complex. *iScience* **25** 105321. (<https://doi.org/10.1016/j.isci.2022.105321>)
- Zhang B, Liu C, Yang Z, *et al.* 2023a Discovery of BWA-522, a first-in-class and orally bioavailable PROTAC degrader of the androgen receptor targeting N-terminal domain for the treatment of prostate cancer. *J Med Chem* **66** 11158–11186. (<https://doi.org/10.1021/acs.jmedchem.3c00585>)
- Zhang F, Biswas M, Massah S, *et al.* 2023b Dynamic phase separation of the androgen receptor and its coactivators key to regulate gene expression. *Nucleic Acids Res* **51** 99–116. (<https://doi.org/10.1093/nar/gkac1158>)
- Zhu P, Baek SH, Bourk EM, *et al.* 2006 Macrophage/cancer cell interactions mediate hormone resistance by a nuclear receptor derepression pathway. *Cell* **124** 615–629. (<https://doi.org/10.1016/j.cell.2005.12.032>)
- Zhu J, Salvatella X & Robustelli P 2022 Small molecules targeting the disordered transactivation domain of the androgen receptor induce the formation of collapsed helical states. *Nat Commun* **13** 6390. (<https://doi.org/10.1038/s41467-022-34077-z>)