Published in final edited form as:

Curr Opin Endocr Metab Res. 2020 February ; 10: 16–22. doi:10.1016/j.coemr.2020.02.006.

Resistance Mechanisms to Taxanes and PARP Inhibitors in Advanced Prostate Cancer

Alan P Lombard^a, Allen C Gao^{a,b,c}

^aDepartment of Urologic Surgery, University of California, Davis, CA, USA.

^bUC Davis Comprehensive Cancer Center, University of California, Davis, CA, USA.

^cVA Northern California Health Care System Sacramento, CA, USA.

Abstract

The clinical landscape concerning advanced prostate cancer is rapidly changing and reaching beyond androgen deprivation therapy and androgen receptor targeted therapies. Taxane chemotherapy is a critical tool in the management of advanced prostate cancer. Additionally, novel drug classes such as PARP inhibitors are being investigated. Despite tremendous progress, resistance to therapy remains as a major impediment to further improvement. Resistance mechanisms appear diverse and are not fully known or understood. This review will highlight recent advances in research regarding mechanisms of resistance to both taxanes (such as increased drug efflux capacity) and PARP inhibitors (such as reversion mutations which restore DNA-repair proficiency). Understanding resistance to therapy promises to remove barriers blocking progress toward improved patient outcomes.

Keywords

Taxane; Docetaxel; Cabazitaxel; PARP inhibitor; Olaparib; Resistance

1. Introduction

Despite tremendous progress in the field of prostate cancer treatment, advanced disease remains incurable. Prostate tumors largely depend on the androgen receptor (AR) for growth and survival. Thus, much effort has been given toward understanding the role of the AR in prostate cancer and targeting the AR either with androgen-deprivation therapy (ADT) or next generation anti-androgens (NGAT) including abiraterone, enzalutamide, apalutamide,

Corresponding Author: Allen C Gao, acgao@ucdavis.edu, Mailing Address: Department of Urologic Surgery, School of Medicine, University of California, Davis, Research III Bldg, Suite 1300, 4645 2nd Ave, Sacramento, CA 95817.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

and darolutamide. However, resistance to AR-targeted therapies occurs frequently and the mechanisms underlying treatment resistance have been extensively studied.

Although AR-targeted therapy is the mainstay in the management of advanced prostate cancer, taxane-based chemotherapy makes up a significant portion of available treatments [1]. Taxanes work by stabilizing microtubules, thus preventing depolymerization and disrupting critical functions needed for cell survival. Docetaxel was first approved in 2004 for the treatment of metastatic castration-resistant prostate cancer but has since also been studied for the treatment of hormone-sensitive prostate cancer in conjunction with ADT. Cabazitaxel, a next generation taxane, was later approved in 2010 for use in docetaxel pre-treated patients. Both of these agents are routinely used in clinical practice and have greatly improved outcomes, but patients still succumb to disease, largely due to the presence or development of resistance which will be later discussed.

Novel drugs are needed to continue to extend survival times for prostate cancer patients. PARP inhibitors (PARPi) are an exciting, emerging drug class for the treatment of prostate cancer. PARPi's are thought to induce undue DNA repair stress, leading to synthetic lethality in tumors which harbor mutations in repair machinery [2]. 20% of prostate tumors harbor such mutations, making this an attractive therapeutic possibility for many patients [3]. While not yet approved, clinical trial data has shown great promise and olaparib, rucaparib, and niraparib have all received FDA breakthrough therapy designation. However, there is still much we don't understand regarding response to PARPi's, nor do we completely understand how resistance may arise to these agents.

Understanding and targeting resistance mechanisms will lead to breakthroughs in prostate cancer treatment. Here we review current research, primarily focusing on studies from the past two years, in the areas of resistance to either taxane or PARPi drugs. We discuss recent efforts to understand the mechanisms of resistance, strategies to overcome them, and methods to detect drug sensitivity in patients.

2. The Role of AR in Taxane Efficacy and Resistance

Taxanes are thought to partially function via inhibition of AR translocation to the nucleus, thus inhibiting AR signaling. It has been postulated that one mechanism of taxane resistance could be increased expression of AR-variants which no longer require microtubule assisted localization to the nucleus. Indeed, recent reports suggest that AR-v7 and AR-v567es may mediate resistance to both docetaxel and cabazitaxel [4, 5]. However, these studies conflict with another report which demonstrates that AR-v7 does not induce resistance to taxanes [6]. Furthermore, two independent studies found no evidence for increased AR-variant expression in models of taxane resistant prostate cancer [6, 7].

Clinical evidence for AR-variant contribution to taxane sensitivity is also unclear. Two independent studies demonstrated no significant association between AR-v7 expression in circulating tumor cells and efficacy of taxanes [8, 9]. A third study testing AR-v7 expression from patient derived exosomes also supports a lack of association between AR-v7 and taxane efficacy [10]. In contrast to these reports, a recent study by Tagawa et al. found that

both AR-v7 and ARv567es clinical detection does suggest a worse outcome when undergoing taxane treatment [11]. They also note that previous studies mentioned above show similar trends as their study but may have been under-powered to show a more robust difference.

In contrast to taxanes, NGAT efficacy has been repeatedly shown to correlate with the presence of AR-variants and furthermore, AR-variants are thought to have potential for stratifying patients between AR-directed therapies and taxane treatment [12]. While more research is needed to fully understand the role of the AR in mediating resistance to taxanes, it is clear that AR expression is at best, a modest factor in determining taxane sensitivity. There remains an urgent need to both uncover clinically relevant mechanisms of taxane resistance and develop appropriate biomarkers to predict taxane sensitivity.

3. Mechanisms of Taxane Resistance Beyond the AR

Taxane chemotherapy is a cornerstone of prostate cancer management. However, resistance to taxanes is common and remains an impediment to further progress. Currently, there are no approved treatments to overcome taxane resistance nor are there clinically validated biomarkers of taxane sensitivity, and whether the mechanisms which mediate resistance to either docetaxel or cabazitaxel are similar is incompletely understood. Below, we review current knowledge regarding resistance to taxanes.

3.1. Taxane Intracellular Accumulation: Drug Efflux and Influx

Overexpression of drug efflux proteins, such as ABCB1, confer a multi-drug resistant state. A recent report demonstrated that overexpressed ABCB1 mediates cross-resistance between docetaxel and cabazitaxel [13]. The role of ABCB1 in mediating cabazitaxel resistance was further substantiated by a second report utilizing models of cabazitaxel resistance post docetaxel treatment [14]. Studies have demonstrated the potential of blocking ABCB1 function to enhance taxane efficacy through the use of small molecule drugs such as elacridar and even anti-androgen drugs such as enzalutamide [13, 15].

While efflux of taxane drugs has been shown to be involved in their efficacy, intra-cellular accumulation via uptake of taxanes is also thought to play a role in sensitivity [16]. The influx transporter SLCO1B3 was shown to be responsible for uptake of both docetaxel and cabazitaxel, and downregulation of SLCO1B3 is seen in a PDX model of taxane resistant prostate cancer [17]. Furthermore, it was shown that SLCO1B3 regulates taxane sensitivity. While clinical translation of targeting drug efflux and accumulation has not yet been achieved, further research may see these strategies to fruition.

3.2. Non-coding RNA Mediated Resistance: Emphasis on microRNAs

The involvement of non-coding RNAs, most notably microRNAs (miRNAs), has garnered much attention in regard to taxane resistance. A study by Gao et al. demonstrated that increased expression of miR-323 in a docetaxel resistant PC3 model induced taxane resistance through regulation of p73 [18]. Armstrong et al. showed that overexpression of miR-181a occurs in taxane resistant C4-2B and DU145 models [19]. Overexpression of miR-181a was shown to decrease sensitivity to both docetaxel and cabazitaxel while

inhibiting miR-181a expression was shown to do the opposite. Down-regulation of both miR-27b and miR-34a was seen in PC3 and DU145 docetaxel resistant models [20]. Furthermore, both miR-27b and miR-34a were shown to inhibit EMT through direct targeting of ZEB1 and to promote sensitivity to docetaxel. In a separate study using similar models, EMT was again associated with the development of resistance, and appeared to rely upon down-regulation of miR-200c and miR-205 [21]. Furthermore, these authors note that re-expression of either miRNA reversed the EMT phenotype and induced apoptosis in docetaxel resistant cells. Efforts to more comprehensively study miRNA involvement in taxane resistance have also been performed. Lin et al. utilized a high-throughput screening methodology to discover miRNAs which may promote or inhibit taxane sensitivity [22]. It was found that miR-217 and miR-181b-5p could increase PC3 cell response to taxanes. Beyond miRNAs, long noncoding RNAs (lncRNAs) may also be active in prostate cancer and resistance to treatment. Ma et al. found that lncRNA DANCR was overexpressed in models of docetaxel resistant prostate cancer, which mediated resistance through regulation of the miR-34a-5p/JAG1 axis [23]. Future studies like those discussed enhance our understanding of taxane resistance and may lead to novel therapeutic strategies.

3.3. Contribution of Autophagy and Altered Metabolism to Taxane Resistance

Docetaxel has been recently shown to induce autophagy in models of prostate cancer, and it is thought that autophagy can be protective and confer taxane resistance [24–26]. Zeng et al. present data to suggest that the oncogene PrLZ can suppress autophagy leading to taxane resistance [25]. Another study suggests that inhibition of docetaxel induced autophagy using tea polyphenols could enhance docetaxel efficacy [26]. It appears that targeting autophagy may prove beneficial in combating taxane resistance, but it should be noted that recent results of the PANDORA trial failed to show that autophagy inhibition using pantoprazole meaningfully enhanced docetaxel treatment [27].

Studies also suggest that altered metabolic pathways participate in resistance to taxanes. It was recently shown that PC3 and DU145 docetaxel resistant cell derivatives up-regulate lipid biosynthesis which could be overcome with orlistat [28]. They and another group demonstrate that the combination of orlistat or TVB-3166, both FASN inhibitors, with taxanes produces greater effect than either agent alone [28, 29]. It is also thought that lactate dehydrogenase may be involved in taxane sensitivity [30, 31]. Thus, targeting metabolic reprogramming in resistant tumors may be an efficacious treatment.

3.4. The Tumor Microenvironment May Promote Taxane Resistance

Beyond tumor cells, the tumor microenvironment also appears active in mediating resistance to therapy. Two recent reports argue that adipose stromal cells are recruited to prostate tumors and may promote a more aggressive phenotype [32, 33]. Furthermore, it was shown that adipose stromal cells can induce EMT and resistance to taxanes in prostate tumor cells [33]. Interestingly, CD4+ T cell infiltration was shown to be higher in docetaxel treated tumors versus adjacent noncancerous tissue [34]. This study also suggests that CCL5 derived from CD4+ T cells may be involved in taxane resistance. These studies highlight the potential key role played by the tumor microenvironment and provide potential novel therapeutic targets.

3.5. Additional Roads to Taxane Resistance

The mechanisms of taxane resistance appear diverse and numerous. A particularly interesting study by Garrido et al. highlight for the first time the role of FKBP7 in prostate cancer and taxane resistance [35]. Their work shows that FKBP7 is upregulated in docetaxel and cabazitaxel resistant derivatives from four separate cell line models. They go on to show that FKBP7 expression correlates with recurrence on docetaxel treatment and that targeting FKBP7 may provide an attractive therapeutic option for taxane resistant tumors. It is also thought that altered expression of tubulin isoforms may mediate resistance to taxanes. A study by Sekino et al. recently demonstrated that models of both docetaxel and cabazitaxel resistant prostate cancer up-regulate TUBB3, which can be targeted to sensitize resistant cells to treatment [36]. As noted in previous sections, EMT appears to be a major driver of docetaxel resistance. Hanrahan et al. reported induction of EMT in PC3 and DU145 docetaxel resistant cells mediated by increased expression of ZEB1. Inhibition of ZEB1 resensitized resistant cells to docetaxel treatment and immunohistochemistry demonstrated increased ZEB1 in prostate tumor tissue post docetaxel treatment [37]. Chen et al. demonstrate down-regulation of INPP4B in similar models, which is shown to mediate resistance and regulate EMT, again suggesting a potential role for EMT in taxane treatment resistance [38]. Recent efforts also suggest the involvement of epigenetic modifications, activation of ERK or PI3K/AKT pathways, activation of Notch signaling, inactivation of apoptosis via increased MCL1 expression, and chemokine signaling in taxane resistance [39–44].

4. PARPi Treatment and Resistance in Prostate Cancer

PARPi's, such as olaparib, are a novel class of drugs with great potential to augment our ability to extend prostate cancer patient survival. The TOPARP-A clinical trial recently demonstrated a high concordance of olaparib sensitivity with those patients harboring mutations in a panel of DNA-repair genes [2]. These data were extended in recent analysis from TOPARP-B, while the TRITON2 and GALAHAD studies demonstrate similar findings with the PARPi's rucaparib and niraparib respectively. Stratification of patients based on DNA-repair gene status promises to improve treatment for a subset of patients, but two things must be addressed; 1) all patients had been heavily pre-treated and, 2) DNA-repair biomarker stratification was insufficient to predict all responses. The second point suggests that additional factors may influence response to PARPi's. Additionally, acquired resistance to PARP inhibition is poorly understood.

To address these unmet needs, recent studies have undertaken the study of response and resistance to PARPi's. In addition to DNA-repair defects outlined in the studies above, a study published by Zimmermann et al. demonstrated a potential new subset of PARPi sensitive patients exhibiting defects in ribonucleotide excision repair [45]. It was also shown that loss of CHD1, a common event in prostate cancer, may confer sensitivity to PARPi treatment [46]. Interestingly, a key mechanism of resistance to PARPi's appears to be reversion mutations of DNA-repair genes. In two distinct studies, it was found that reversion mutations restoring functional proteins were found in PARPi resistant patients, including mutations in BRCA2 and PALB2 [47, 48]. A recent clinical case study recently

demonstrated emergence of neuroendocrine-like features post olaparib failure with no evidence of reversion mutations or restoration of DNA-repair [49]. Thus, it is possible that treatment-induced neuroendocrine disease may be involved in olaparib resistance. Li et al. show that Plk1, known to be overexpressed in prostate tumors, may be involved in resistance to olaparib [50]. NPRL2 is also thought to mediate resistance to olaparib in prostate cancer [51]. As the use of PARPi's is new in the context of prostate cancer, it is useful to also include putative mechanisms of PARPi resistance from other indications, which may also be relevant in prostate tumors. It was recently demonstrated that HMGA2 can physically interact with PARP1 and can both enhance its PARylation ability and decrease the ability of PARPi's to trap PARP on DNA, which may lead to treatment resistance [52]. As HMGA2 is thought to serve as an oncogene in some prostate tumors, future studies should be geared at assessing its role in PARPi resistance. It is also postulated that restoration of homologous recombination potential via decreased expression of 53BP1 may lead to the development of PARPi resistance [53]. Overall, little is known regarding the development of PARPi resistance and it may be useful to explore putative combination therapies to enhance PARPi efficacy upfront. A recent study demonstrated that a PARPi in combination with a cyclin dependent kinase inhibitor has increased ability to decrease viability of prostate cancer cells and tumors [54]. This and other combinations may prove to be highly beneficial treatment strategies.

The first point above regarding pre-treatment of patients was recently addressed by a study testing olaparib in CRPC models of enzalutamide, abiraterone, and taxane resistance [55]. It was shown that only taxane resistant cells exhibited robust cross-resistance to olaparib, which was shown to be mediated by overexpression of ABCB1. It has been shown that a secondary mechanism of action of PARPi's may be through inhibition of AR signaling [56]. Whether AR expression is linked to PARPi sensitivity remains an open question. However, in the above mentioned study, cell line models of enzalutamide and abiraterone resistance, both of which display increased AR and AR-variant expression, remain relatively sensitive to olaparib [55]. Additional study will aid the successful approval and translation of PARPi treatments for prostate cancer.

5. Understanding Biomarkers of Efficacy to Enhance Treatment Response

As we learn more about sensitivity and resistance to available treatments, it becomes increasingly important to develop biomarkers and patient monitoring strategies capable of stratifying patients for treatment. We've highlighted research demonstrating the potential of using AR-variants to stratify between AR-directed therapies and taxane treatment. Methodologies to study potential biomarkers from cell-free DNA (cfDNA), circulating tumor cells, patient serum and even exosomes are being developed and have shown great promise. Wyatt et al. recently demonstrated that assaying circulating tumor DNA was sufficient to detect all driver mutations identified in matched tumor biopsies in most patients [57]. Subsequent analysis of cfDNA from the TOPARP-A trial demonstrated that mutations associated with olaparib sensitivity could be detected, suggesting that patients could be stratified and monitored for response to PARPi's [47]. Thus, future studies promise to add biomarkers to improve treatment strategies.

6. Conclusions

Resistance to therapy is an unfortunate and seemingly inevitable occurrence in the management of advanced cancer. As we learn more about resistance mechanisms, improved treatment sequences can be developed which may avoid using therapies where they are likely to fail. It will also be imperative to continue testing therapeutic combination approaches to avoid the development of resistance over time. Future efforts promise to enhance our understanding of treatment resistance and extend patient survival times.

Funding Sources

This work was supported in part by grants NIH/NCI CA168601, CA179970, CA225836, DOD PC150229, DOD PC150040, and the U.S. Department of Veterans Affairs, Office of Research & Development BL&D grant number I01BX0002653 (A.C. G), and a Research Career Scientist Award (A.C.G).

References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest

- [1]. Tsao CK, Cutting E, Martin J and Oh WK. The role of cabazitaxel in the treatment of metastatic castration-resistant prostate cancer. *Ther Adv Urol* 2014; 6: 97–104. [PubMed: 24883107]
- [2]. Mateo J, Carreira S, Sandhu S, Miranda S, Mossop H, Perez-Lopez R, Nava Rodrigues D, Robinson D, Omlin A, Tunariu N, Boysen G, Porta N, Flohr P, Gillman A, Figueiredo I, Paulding C, Seed G, Jain S, Ralph C, Protheroe A, Hussain S, Jones R, Elliott T, McGovern U, Bianchini D, Goodall J, Zafeiriou Z, Williamson CT, Ferraldeschi R, Riisnaes R, Ebbs B, Fowler G, Roda D, Yuan W, Wu YM, Cao X, Brough R, Pemberton H, A'Hern R, Swain A, Kunju LP, Eeles R, Attard G, Lord CJ, Ashworth A, Rubin MA, Knudsen KE, Feng FY, Chinnaiyan AM, Hall E and de Bono JS. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. *N Engl J Med* 2015; 373: 1697–1708. [PubMed: 26510020]
- [3]. Mateo J, Boysen G, Barbieri CE, Bryant HE, Castro E, Nelson PS, Olmos D, Pritchard CC, Rubin MA and de Bono JS. DNA Repair in Prostate Cancer: Biology and Clinical Implications. *Eur Urol* 2017; 71: 417–425. [PubMed: 27590317]
- [4]. Thadani-Mulero M, Portella L, Sun S, Sung M, Matov A, Vessella RL, Corey E, Nanus DM, Plymate SR and Giannakakou P. Androgen receptor splice variants determine taxane sensitivity in prostate cancer. *Cancer Res* 2014; 74: 2270–2282. [PubMed: 24556717]
- [5]. Zhang G, Liu X, Li J, Ledet E, Alvarez X, Qi Y, Fu X, Sartor O, Dong Y and Zhang H. Androgen receptor splice variants circumvent AR blockade by microtubule-targeting agents. *Oncotarget* 2015; 6: 23358–23371. [PubMed: 26160840]
- *[6]. Lombard AP, Liu L, Cucchiara V, Liu C, Armstrong CM, Zhao R, Yang JC, Lou W, Evans CP and Gao AC. Intra versus Inter Cross-resistance Determines Treatment Sequence between Taxane and AR-Targeting Therapies in Advanced Prostate Cancer. *Mol Cancer Ther* 2018; 17: 2197–2205. [PubMed: 29891490] Utilizing models of enzalutamide, abiraterone, and taxane resistant CRPC, authors demonstrate a lack of cross-resistance between NGAT's and taxane drugs. However, cross-resistance does exist between enzalutamide and abiraterone and separately between docetaxel and cabazitaxel. This study suggests drugs of each class can be safely sequenced with those of the other class and suggest that mechanisms of resistance vary between NGAT's and taxanes.
- [7]. Shiota M, Dejima T, Yamamoto Y, Takeuchi A, Imada K, Kashiwagi E, Inokuchi J, Tatsugami K, Kajioaka S, Uchiumi T and Eto M. Collateral resistance to taxanes in enzalutamide-resistant prostate cancer through aberrant androgen receptor and its variants. *Cancer Sci* 2018; 109: 3224–3234. [PubMed: 30051622]

- *[8]. Antonarakis ES, Lu C, Lubner B, Wang H, Chen Y, Nakazawa M, Nadal R, Paller CJ, Denmeade SR, Carducci MA, Eisenberger MA and Luo J. Androgen Receptor Splice Variant 7 and Efficacy of Taxane Chemotherapy in Patients With Metastatic Castration-Resistant Prostate Cancer. *JAMA Oncol* 2015; 1: 582–591. [PubMed: 26181238] Authors demonstrate that mRNA detection of AR-v7 in patient circulating tumor cells does not correlate with response to taxane treatment. Furthermore, AR-v7 positive patients appeared to fare better on taxane treatment over NGAT treatment. Thus, it was concluded that AR-v7 may have potential to serve as a treatment selection biomarker.
- [9]. Onstenk W, Sieuwerts AM, Kraan J, Van M, Nieuweboer AJ, Mathijssen RH, Hamberg P, Meulenbeld HJ, De Laere B, Dirix LY, van Soest RJ, Lolkema MP, Martens JW, van Weerden WM, Jenster GW, Foekens JA, de Wit R and Sleijfer S. Efficacy of Cabazitaxel in Castration-resistant Prostate Cancer Is Independent of the Presence of AR-V7 in Circulating Tumor Cells. *Eur Urol* 2015; 68: 939–945. [PubMed: 26188394]
- [10]. Del Re M, Biasco E, Crucitta S, Derosa L, Rofi E, Orlandini C, Miccoli M, Galli L, Falcone A, Jenster GW, van Schaik RH and Danesi R. The Detection of Androgen Receptor Splice Variant 7 in Plasma-derived Exosomal RNA Strongly Predicts Resistance to Hormonal Therapy in Metastatic Prostate Cancer Patients. *Eur Urol* 2017; 71: 680–687. [PubMed: 27733296]
- *[11]. Tagawa ST, Antonarakis ES, Gjyrezi A, Galletti G, Kim S, Worroll D, Stewart J, Zaher A, Szatrowski TP, Ballman KV, Kita K, Tasaki S, Bai Y, Portella L, Kirby BJ, Saad F, Eisenberger MA, Nanus DM and Giannakakou P. Expression of AR-V7 and ARv(567es) in Circulating Tumor Cells Correlates with Outcomes to Taxane Therapy in Men with Metastatic Prostate Cancer Treated in TAXYNERGY. *Clin Cancer Res* 2019; 25: 1880–1888. [PubMed: 30301829] In contrast to previous work, this study suggests that AR-variants may indicate a worse outcome on taxane treatment, although not as strongly as that to AR-directed therapies. Thus, AR-variants may have a modest role in taxane resistance.
- [12]. Bastos DA and Antonarakis ES. AR-V7 and treatment selection in advanced prostate cancer: are we there yet? *Precis Cancer Med* 2018; 1:
- [13]. Lombard AP, Liu C, Armstrong CM, Cucchiara V, Gu X, Lou W, Evans CP and Gao AC. ABCB1 Mediates Cabazitaxel-Docetaxel Cross-Resistance in Advanced Prostate Cancer. *Mol Cancer Ther* 2017; 16: 2257–2266. [PubMed: 28698198]
- [14]. Machioka K, Izumi K, Kadono Y, Iwamoto H, Naito R, Makino T, Kadomoto S, Natsagdorj A, Keller ET, Zhang J and Mizokami A. Establishment and characterization of two cabazitaxel-resistant prostate cancer cell lines. *Oncotarget* 2018; 9: 16185–16196. [PubMed: 29662635]
- [15]. Zhu Y, Liu C, Armstrong C, Lou W, Sandher A and Gao AC. Antiandrogens Inhibit ABCB1 Efflux and ATPase Activity and Reverse Docetaxel Resistance in Advanced Prostate Cancer. *Clin Cancer Res* 2015; 21: 4133–4142. [PubMed: 25995342]
- [16]. de Morree E, van Soest R, Aghai A, de Ridder C, de Bruijn P, Ghobadi Moghaddam-Helmantel I, Burger H, Mathijssen R, Wiemer E, de Wit R and van Weerden W. Understanding taxanes in prostate cancer; importance of intratumoral drug accumulation. *Prostate* 2016; 76: 927–936. [PubMed: 26997363]
- [17]. de Morree ES, Bottcher R, van Soest RJ, Aghai A, de Ridder CM, Gibson AA, Mathijssen RH, Burger H, Wiemer EA, Sparreboom A, de Wit R and van Weerden WM. Loss of SLCO1B3 drives taxane resistance in prostate cancer. *Br J Cancer* 2016; 115: 674–681. [PubMed: 27537383]
- [18]. Gao Q and Zheng J. microRNA-323 upregulation promotes prostate cancer growth and docetaxel resistance by repressing p73. *Biomed Pharmacother* 2018; 97: 528–534. [PubMed: 29091904]
- [19]. Armstrong CM, Liu C, Lou W, Lombard AP, Evans CP and Gao AC. MicroRNA-181a promotes docetaxel resistance in prostate cancer cells. *Prostate* 2017; 77: 1020–1028. [PubMed: 28485104]
- [20]. Zhang G, Tian X, Li Y, Wang Z, Li X and Zhu C. miR-27b and miR-34a enhance docetaxel sensitivity of prostate cancer cells through inhibiting epithelial-to-mesenchymal transition by targeting ZEB1. *Biomed Pharmacother* 2018; 97: 736–744. [PubMed: 29102917]
- [21]. Puhr M, Hoefer J, Schafer G, Erb HH, Oh SJ, Klocker H, Heidegger I, Neuwirt H and Culig Z. Epithelial-to-mesenchymal transition leads to docetaxel resistance in prostate cancer and is mediated by reduced expression of miR-200c and miR-105. *Am J Pathol* 2012; 181: 2188–2201. [PubMed: 23041061]

- [22]. Lin HM, Nikolic I, Yang J, Castillo L, Deng N, Chan CL, Yeung NK, Dodson E, Elsworth B, Spielman C, Lee BY, Boyer Z, Simpson KJ, Daly RJ, Horvath LG and Swarbrick A. MicroRNAs as potential therapeutics to enhance chemosensitivity in advanced prostate cancer. *Sci Rep* 2018; 8: 7820. [PubMed: 29777112]
- [23]. Ma Y, Fan B, Ren Z, Liu B and Wang Y. Long noncoding RNA DANCER contributes to docetaxel resistance in prostate cancer through targeting the miR-34a-5p/JAG1 pathway. *Onco Targets Ther* 2019; 12: 5485–5497. [PubMed: 31371987]
- [24]. Hu F, Zhao Y, Yu Y, Fang JM, Cui R, Liu ZQ, Guo XL and Xu Q. Docetaxel-mediated autophagy promotes chemoresistance in castration-resistant prostate cancer cells by inhibiting STAT3. *Cancer Lett* 2018; 416: 24–30. [PubMed: 29246644]
- [25]. Zeng J, Liu W, Fan YZ, He DL and Li L. PrLZ increases prostate cancer docetaxel resistance by inhibiting LKB1/AMPK-mediated autophagy. *Theranostics* 2018; 8: 109–123. [PubMed: 29290796]
- [26]. Wang Q, He WY, Zeng YZ, Hossain A and Gou X. Inhibiting autophagy overcomes docetaxel resistance in castration-resistant prostate cancer cells. *Int Urol Nephrol* 2018; 50: 675–686. [PubMed: 29460131]
- [27]. Hansen AR, Tannock IF, Templeton A, Chen E, Evans A, Knox J, Prawira A, Sridhar SS, Tan S, Vera-Badillo F, Wang L, Wouters BG and Joshua AM. Pantoprazole Affecting Docetaxel Resistance Pathways via Autophagy (PANDORA): Phase II Trial of High Dose Pantoprazole (Autophagy Inhibitor) with Docetaxel in Metastatic Castration-Resistant Prostate Cancer (mCRPC). *Oncologist* 2019;
- [28]. Soucek JJ, Davis AL, Hill TK, Holmes MB, Qi B, Singh PK, Kridel SJ and Mohs AM. Combination Treatment with Orlistat-Containing Nanoparticles and Taxanes Is Synergistic and Enhances Microtubule Stability in Taxane-Resistant Prostate Cancer Cells. *Mol Cancer Ther* 2017; 16: 1819–1830. [PubMed: 28615298]
- [29]. Heuer TS, Ventura R, Mordec K, Lai J, Fridlib M, Buckley D and Kemble G. FASN Inhibition and Taxane Treatment Combine to Enhance Anti-tumor Efficacy in Diverse Xenograft Tumor Models through Disruption of Tubulin Palmitoylation and Microtubule Organization and FASN Inhibition-Mediated Effects on Oncogenic Signaling and Gene Expression. *EBioMedicine* 2017; 16: 51–62. [PubMed: 28159572]
- [30]. Hiew K, Hart CA, Ali A, Elliott T, Ramani V, Sangar V, Lau M, Maddineni S, Brown M and Clarke N. Primary Mutational Landscape Linked with Pre-Docetaxel Lactate Dehydrogenase Levels Predicts Docetaxel Response in Metastatic Castrate-Resistant Prostate Cancer. *Eur Urol Focus* 2018;
- [31]. Muramatsu H, Sumitomo M, Morinaga S, Kajikawa K, Kobayashi I, Nishikawa G, Kato Y, Watanabe M, Zennami K, Kanao K, Nakamura K, Suzuki S and Yoshikawa K. Targeting lactate dehydrogenase A promotes docetaxel-induced cytotoxicity predominantly in castration-resistant prostate cancer cells. *Oncol Rep* 2019; 42: 224–230. [PubMed: 31180564]
- [32]. Zhang T, Tseng C, Zhang Y, Sirin O, Corn PG, Li-Ning-Tapia EM, Troncoso P, Davis J, Pettaway C, Ward J, Frazier ML, Logothetis C and Kolonin MG. CXCL1 mediates obesity-associated adipose stromal cell trafficking and function in the tumour microenvironment. *Nat Commun* 2016; 7: 11674. [PubMed: 27241286]
- [33]. Su F, Ahn S, Saha A, DiGiovanni J and Kolonin MG. Adipose stromal cell targeting suppresses prostate cancer epithelial-mesenchymal transition and chemoresistance. *Oncogene* 2019; 38: 1979–1988. [PubMed: 30361686]
- [34]. Xiang P, Jin S, Yang Y, Sheng J, He Q, Song Y, Yu W, Hu S and Jin J. Infiltrating CD4⁺ T cells attenuate chemotherapy sensitivity in prostate cancer via CCL5 signaling. *Prostate* 2019; 79: 1018–1031. [PubMed: 31018021]
- *[35]. Garrido MF, Martin NJ, Bertrand M, Gaudin C, Commo F, El Kalaany N, Al Nakouzi N, Fazli L, Del Nery E, Camonis J, Perez F, Lerondel S, Le Pape A, Compagno D, Gleave M, Lorient Y, Desaubry L, Vagner S, Fizazi K and Chauchereau A. Regulation of eIF4F Translation Initiation Complex by the Peptidyl Prolyl Isomerase FKBP7 in Taxane-resistant Prostate Cancer. *Clin Cancer Res* 2019; 25: 710–723. [PubMed: 30322877] This study demonstrates the functionality of human FKBP7 for the first time. Robust analysis provided demonstrates increased expression

in taxane resistant prostate cancer and a correlation between FKBP7 expression and recurrence. Study further shows the potential utility of targeting FKBP7 in prostate cancer.

- [36]. Sekino Y, Han X, Kawaguchi T, Babasaki T, Goto K, Inoue S, Hayashi T, Teishima J, Shiota M, Yasui W and Matsubara A. TUBB3 Reverses Resistance to Docetaxel and Cabazitaxel in Prostate Cancer. *Int J Mol Sci* 2019; 20:
- [37]. Hanrahan K, O'Neill A, Prencipe M, Bugler J, Murphy L, Fabre A, Pühr M, Culig Z, Murphy K and Watson RW. The role of epithelial-mesenchymal transition drivers ZEB1 and ZEB2 in mediating docetaxel-resistant prostate cancer. *Mol Oncol* 2017; 11: 251–265. [PubMed: 28133913]
- [38]. Chen H, Li H and Chen Q. INPP4B reverses docetaxel resistance and epithelial-to-mesenchymal transition via the PI3K/Akt signaling pathway in prostate cancer. *Biochem Biophys Res Commun* 2016; 477: 467–472. [PubMed: 27318090]
- [39]. Ramachandran K, Speer C, Nathanson L, Claros M and Singal R. Role of DNA Methylation in Cabazitaxel Resistance in Prostate Cancer. *Anticancer Res* 2016; 36: 161–168. [PubMed: 26722040]
- [40]. Hongo H, Kosaka T and Oya M. Analysis of cabazitaxel-resistant mechanism in human castration-resistant prostate cancer. *Cancer Sci* 2018; 109: 2937–2945. [PubMed: 29989268]
- [41]. Qiu S, Deng L, Bao Y, Jin K, Tu X, Li J, Liao X, Liu Z, Yang L and Wei Q. Reversal of docetaxel resistance in prostate cancer by Notch signaling inhibition. *Anticancer Drugs* 2018; 29: 871–879. [PubMed: 29944470]
- [42]. Kapur N, Mir H, Sonpavde GP, Jain S, Bae S, Lillard JW Jr., and Singh S. Prostate cancer cells hyper-activate CXCR6 signaling by cleaving CXCL16 to overcome effect of docetaxel. *Cancer Lett* 2019; 454: 1–13. [PubMed: 30974114]
- [43]. Natsagdorj A, Izumi K, Hiratsuka K, Machioka K, Iwamoto H, Naito R, Makino T, Kadomoto S, Shigehara K, Kadono Y, Lin WJ, Maolake A and Mizokami A. CCL2 induces resistance to the antiproliferative effect of cabazitaxel in prostate cancer cells. *Cancer Sci* 2019; 110: 279–288. [PubMed: 30426599]
- [44]. Handle F, Prekovic S, Helsen C, Van den Broeck T, Smeets E, Moris L, Eerlings R, Kharraz SE, Urbanucci A, Mills IG, Joniau S, Attard G and Claessens F. Drivers of AR indifferent anti-androgen resistance in prostate cancer cells. *Sci Rep* 2019; 9: 13786. [PubMed: 31551480]
- *[45]. Zimmermann M, Murina O, Reijns MAM, Agathangelou A, Challis R, Tarnauskaite Z, Muir M, Fluteau A, Aregger M, McEwan A, Yuan W, Clarke M, Lambros MB, Paneesha S, Moss P, Chandrashekhar M, Angers S, Moffat J, Brunton VG, Hart T, de Bono J, Stankovic T, Jackson AP and Durocher D. CRISPR screens identify genomic ribonucleotides as a source of PARP-trapping lesions. *Nature* 2018; 559: 285–289. [PubMed: 29973717] CRISPR screen demonstrated that mutation in ribonuclease H2 genes sensitized cells to PARPi treatment. It was determined that deficient ribonucleotide excision repair leads to PARPi sensitivity and that the frequent deletion of RNASEH2B in metastatic prostate tumors may represent a new therapeutic window for PARP inhibition.
- [46]. Shenoy TR, Boysen G, Wang MY, Xu QZ, Guo W, Koh FM, Wang C, Zhang LZ, Wang Y, Gil V, Aziz S, Christova R, Rodrigues DN, Crespo M, Rescigno P, Tunariu N, Riisnaes R, Zafeiriou Z, Flohr P, Yuan W, Knight E, Swain A, Ramalho-Santos M, Xu DY, de Bono J and Wu H. CHD1 loss sensitizes prostate cancer to DNA damaging therapy by promoting error-prone double-strand break repair. *Ann Oncol* 2017; 28: 1495–1507. [PubMed: 28383660]
- *[47]. Goodall J, Mateo J, Yuan W, Mossop H, Porta N, Miranda S, Perez-Lopez R, Dolling D, Robinson DR, Sandhu S, Fowler G, Ebbs B, Flohr P, Seed G, Rodrigues DN, Boysen G, Bertan C, Atkin M, Clarke M, Crespo M, Figueiredo I, Riisnaes R, Sumanasuriya S, Rescigno P, Zafeiriou Z, Sharp A, Tunariu N, Bianchini D, Gillman A, Lord CJ, Hall E, Chinnaiyan AM, Carreira S, de Bono JS and investigators T-A. Circulating Cell-Free DNA to Guide Prostate Cancer Treatment with PARP Inhibition. *Cancer Discov* 2017; 7: 1006–1017. [PubMed: 28450425]
- *[48]. Quigley D, Alumkal JJ, Wyatt AW, Kothari V, Foye A, Lloyd P, Aggarwal R, Kim W, Lu E, Schwartzman J, Beja K, Annala M, Das R, Diolaiti M, Pritchard C, Thomas G, Tomlins S, Knudsen K, Lord CJ, Ryan C, Youngren J, Beer TM, Ashworth A, Small EJ and Feng FY. Analysis of Circulating Cell-Free DNA Identifies Multiclonal Heterogeneity of BRCA2

Reversion Mutations Associated with Resistance to PARP Inhibitors. *Cancer Discov* 2017; 7: 999–1005. [PubMed: 28450426] Two independent studies (ref 47 and 48) determine that cfDNA can be used to assess PARPi resistance mechanisms, including reversion mutations which restore DNA repair. It was also determined that PARPi resistance mechanisms are heterogenous and thus can be missed by individual solid tissue biopsies.

- [49]. Horak P, Weischenfeldt J, von Amsberg G, Beyer B, Schutte A, Uhrig S, Geldon L, Klink B, Feuerbach L, Hubschmann D, Kreutzfeldt S, Heining C, Maier S, Hutter B, Penzel R, Schlesner M, Eils R, Sauter G, Stenzinger A, Brors B, Schrock E, Glimm H, Frohling S and Schlomm T. Response to olaparib in a PALB2 germline mutated prostate cancer and genetic events associated with resistance. *Cold Spring Harb Mol Case Stud* 2019; 5:
- [50]. Li J, Wang R, Kong Y, Broman MM, Carlock C, Chen L, Li Z, Farah E, Ratliff TL and Liu X. Targeting Plk1 to Enhance Efficacy of Olaparib in Castration-Resistant Prostate Cancer. *Mol Cancer Ther* 2017; 16: 469–479. [PubMed: 28069876]
- [51]. Chen X, Chen Z, Zheng B and Tang W. Targeting NPRL2 to enhance the efficacy of Olaparib in castration-resistant prostate cancer. *Biochem Biophys Res Commun* 2019; 508: 620–625. [PubMed: 30522863]
- [52]. Hombach-Klonisch S, Kalantari F, Medapati MR, Natarajan S, Krishnan SN, Kumar-Kanojia A, Thanasupawat T, Begum F, Xu FY, Hatch GM, Los M and Klonisch T. HMGA2 as a functional antagonist of PARP1 inhibitors in tumor cells. *Mol Oncol* 2019; 13: 153–170. [PubMed: 30289618]
- [53]. Hong R, Ma F, Zhang W, Yu X, Li Q, Luo Y, Zhu C, Jiang W and Xu B. 53BP1 depletion causes PARP inhibitor resistance in ATM-deficient breast cancer cells. *BMC Cancer* 2016; 16: 725. [PubMed: 27613518]
- [54]. Liu B, Li L, Yang G, Geng C, Luo Y, Wu W, Manyam GC, Korentzelos D, Park S, Tang Z, Wu C, Dong Z, Sigouros M, Sboner A, Beltran H, Chen Y, Corn PG, Tetzlaff MT, Troncoso P, Broom B and Thompson TC. PARP Inhibition Suppresses GR-MYC-CDK5-RB1-E2F1 Signaling and Neuroendocrine Differentiation in Castration-Resistant Prostate Cancer. *Clin Cancer Res* 2019; 25: 6839–6851. [PubMed: 31439587]
- [55]. Lombard AP, Liu C, Armstrong CM, D'Abronzio LS, Lou W, Chen H, Dall'Era M, Ghosh PM, Evans CP and Gao AC. Overexpressed ABCB1 Induces Olaparib-Taxane Cross-Resistance in Advanced Prostate Cancer. *Transl Oncol* 2019; 12: 871–878. [PubMed: 31075528]
- [56]. Schiewer MJ, Goodwin JF, Han S, Brenner JC, Augello MA, Dean JL, Liu F, Planck JL, Ravindranathan P, Chinnaiyan AM, McCue P, Gomella LG, Raj GV, Dicker AP, Brody JR, Pascal JM, Centenera MM, Butler LM, Tilley WD, Feng FY and Knudsen KE. Dual roles of PARP-1 promote cancer growth and progression. *Cancer Discov* 2012; 2: 1134–1149. [PubMed: 22993403]
- *[57]. Wyatt AW, Annala M, Aggarwal R, Beja K, Feng F, Youngren J, Foye A, Lloyd P, Nykter M, Beer TM, Alumkal JJ, Thomas GV, Reiter RE, Rettig MB, Evans CP, Gao AC, Chi KN, Small EJ and Gleave ME. Concordance of Circulating Tumor DNA and Matched Metastatic Tissue Biopsy in Prostate Cancer. *J Natl Cancer Inst* 2017; 109: Wyatt et al demonstrate that all driver mutations identified in solid biopsies can be detected in cfDNA liquid biopsies in most patients sampled. Furthermore, additional alterations not present in solid biopsies could be detected in liquid biopsies. This study highlights the exciting potential to monitor patient disease burden in a relatively non-invasive manner.