The Emergence of Precision Urologic Oncology: A Collaborative Review on Biomarker-driven Therapeutics

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Abstract

Context—Biomarker-driven cancer therapy, also referred to as precision oncology, has received increasing attention for its promise of improving patient outcomes by defining subsets of patients more likely to respond to various therapies.

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Precision medicine has the highest potential to impact the care of patients, and major strides have been made in urologic oncology. Prospective clinical trials will define reliable predictive biomarkers and new therapeutic targets leading to real improvement in patient outcomes.

Objective—In this collaborative review article, we examine recent literature regarding biomarker-driven therapeutics in urologic oncology, to better define the state of the field, explore the current evidence supporting utility of this approach, and gauge potential for the future.

Evidence acquisition—We reviewed relevant literature, with a particular focus on recent studies about targeted therapy, predictors of response, and biomarker development.

Evidence synthesis—The recent advances in molecular profiling have led to a rapid expansion of potential biomarkers and predictive information for patients with urologic malignancies. Across disease states, distinct molecular subtypes of cancers have been identified, with the potential to inform choices of management strategy. Biomarkers predicting response to standard therapies (such as platinum-based chemotherapy) are emerging. In several malignancies (particularly renal cell carcinoma and castration-resistant prostate cancer), targeted therapy against commonly altered signaling pathways has emerged as standard of care. Finally, targeted therapy against alterations present in rare patients (less than 2%) across diseases has the potential to drastically alter patterns of care and choices of therapeutic options.

Conclusions—Precision medicine has the highest potential to impact the care of patients. Prospective studies in the setting of clinical trials and standard of care therapy will help define reliable predictive biomarkers and new therapeutic targets leading to real improvement in patient outcomes.

Patient summary—Precision oncology uses molecular information (DNA and RNA) from the individual and the tumor to match the right patient with the right treatment. Tremendous strides have been made in defining the molecular underpinnings of urologic malignancies and understanding how these predict response to treatment—this represents the future of urologic oncology.

Keywords

1. Introduction

The past decade has seen an explosion of therapeutic options in urologic oncology, across multiple cancer types. Renal cell carcinoma (RCC) patients now have options of tyrosine kinase inhibitors, mechanistic target of rapamycin (mTOR) inhibitors, and immunotherapy agents. The prostate cancer field has seen the approval of over half a dozen novel agents in the past few years, as well as shifting paradigms regarding the temporal sequencing of agents [1,2]. Urothelial carcinoma, in addition to defining subsets of patients with best response to standard of care chemotherapeutic options, appears poised for novel agents to make meaningful impact as well. Clearly, this is an exciting time to be in urologic oncology, as there is more promise and hope for our patients than ever before.

Each novel therapy improves outcomes compared with previous generations of standard therapy, but unfortunately, the recent improvements in patient survival can be described as incremental rather than transformative. However, defined subsets of patients respond well to each therapy, and it is likely that these subsets of responders are not the same for all different

therapeutic options. The example of trastuzumab (Herceptin) in breast cancer treatment may serve as a model for successful development of precision medicine approaches. Trastuzumab was the first rationally designed targeted therapy for solid tumors, based on the discovery that some breast cancers have a high degree of amplification of *Her2/neu* [3], and that these cancers are associated with worse prognosis [4]. Development of the drug from bench to approval spanned 13 yr—and it has now been responsible for a dramatic change in outcome for women for this subtype of breast cancer.

In urologic oncology, now comes the challenge of taking these diverse therapeutic opportunities, and finding ways to match the right therapy with the right patient: the paradigm of precision medicine. In this review we will explore the history, challenges, and opportunities inherent in this process, and explore the future of biomarker-driven therapeutics in urologic oncology.

Biomarker-driven therapy can refer to multiple approaches to patient stratification and selection of management strategies. First, this can refer to classic targeted therapy, in which a specific gene product serves as both the biomarker and the target of therapeutic action— *HER2* overexpression in breast cancer, or *BRAF* mutations in melanoma, are classic examples [5]. Secondly, biomarkers may distinguish patients that are preferentially sensitive (or resistant) to standard therapeutic options, even though these specific biomarkers are not targets themselves (such as triple negative breast cancer or *KRAS* mutated colorectal cancers). Finally, distinct subclasses of cancers may respond in fundamentally different manners to various therapeutic interventions—many such subclasses may be identifiable using histologic criteria, but others may only be exposed using specific molecular biomarkers. We will review these concepts across urologic oncology in a relatively disease-specific manner. In addition, we will also discuss issues that apply more universally, across multiple malignancies and multiple signaling pathways. These include concepts of utilizing biomarker-driven stratification to determine sequencing of different therapeutic options, implications of tumor heterogeneity for biomarker-driven therapeutics, and the impact of novel approaches such an immunotherapy.

The foundations this field is based upon have undergone major advances with the advent of novel technologies for molecular profiling of tumor and patient tissue, including next-generation sequencing of DNA and RNA, improved understanding and profiling of epigenetics, and advanced proteomic analysis. Biomarkers can be defined using DNA sequencing (targeted or unbiased exome/genome-wide approaches), transcriptome profiling (RNA-sequencing or microarray-based gene expression), and in-situ techniques like immunohistochemistry or RNA in-situ hybridization to define protein and expression and localization [6,7]. Application of these technologies, including systematic studies as part of the International Cancer Genome Consortium and The Cancer Genome Atlas projects, has led to a massive expansion of the catalog of known alterations in urologic oncology, the starting point for defining biomarkers with real relevance for clinical care.

2. Evidence acquisition

Medline and Google Scholar searches were conducted to identify original articles, review articles, editorials, and presented abstracts addressing biomarker driven therapeutics in urologic malignancies. Keywords included "biomarker," "targeted therapy," "predictors of response," "therapy resistance," and "heterogeneity." We limited our initial search to studies and investigations published from January 2005 to January 2016. References cited in selected articles and in review articles retrieved in our search were also used to identify manuscripts that were not included in the initial search. Links to related articles and cross-reading of citations in related articles were surveyed. The articles that provided the highest level of evidence were then evaluated and selected with the consensus of authors. A total of 103 articles were reviewed. This collaborative review is the result of an interactive peer-reviewing process by the panel of coauthors.

3. Evidence synthesis

3.1 Targeted therapies in urologic oncology

3.1.1 Androgen signaling in prostate cancer—The oldest form of *targeted therapy* in urology (and perhaps in all of oncology) came with the recognition that ablation of androgens via surgical castration resulted in regression of advanced prostate cancer. Although not often thought of as targeted therapy, the dependence of prostate cancer on androgen signaling forms the basis of the historical and current approach to advanced prostate cancer, with androgen ablation representing the mainstay of treatment for the disease. The more recent discovery that castration-resistant prostate cancer (CRPC) largely maintains its dependency on androgen signaling further underscores the central importance of this signaling axis, and multiple novel therapeutics rely on improved targeting of androgen signaling over and beyond that which can be achieved using surgical castration or convention androgen-deprivation therapy approaches. These include further reductions of androgen production by targeting synthetic enzymes such as CYP17, the target of abiraterone acetate (Zytiga), and improved inhibition of the androgen receptor itself (enzalutamide/Xtandi, ARN-509/apalutamide) and downstream effects on transcription, proliferation, and survival of prostate cancer cells. These approaches have been reviewed elsewhere [8,9].

A critical question for these next-generation antiandrogen agents going forward is determining the patients that will most benefit from their use. Deregulation of the androgen signaling axis is common in prostate cancer [6], and alterations in the *AR* gene itself become highly prevalent in CRPC [10]. These include amplification of the *AR* gene, point mutations, and splice variants. The impact of these alterations on response to antiandrogen therapy remains unclear, and this is a major focus of ongoing clinical and preclinical investigation.

Mutations and gene amplifications in the *AR* gene itself have long been known to emerge and promote resistance in the setting of conventional androgen ablation [11–13]. However, implications of these genomic events for patient response to newer agents like enzalutamide and abiraterone are less clear, and data has only recently begun to emerge. Several studies

suggest that *AR* amplification and mutation are more common in patients progressing on these therapies compared with responders [14], and there are suggestions that amplification of *AR* can predict response to both enzalutamide and abiraterone [15,16]. Preclinical models have shown that constitutively active, truncated androgen receptor splice variants can continue to drive androgen signaling in CRPC cells, and that this activity can promote resistance to enzalutamide [17]. Clinical studies have also reported that the presence of one such androgen receptor splice variant in circulating tumor cells from patients with CRPC is correlated with resistance to second-generation androgen targeting agents [18], and may emerge during therapy [19]. Across all these questions, larger, rigorously conductive clinical studies and correlative genomic analysis will be necessary to provide definitive answers.

3.1.2 Neuroendocrine prostate cancer—A subset of CRPC transitions from *AR* dependence to an *AR* indifferent state. These CRPC-neuroendocrine cancers have been also referred to as neuroendocrine prostate cancer and anaplastic cancer [20,21]. This is a highly aggressive form of CRPC that may emerge in the setting of prolonged androgen-targeting therapy [22]. Improved characterization of this entity at the clinical, histological, and molecular level is ongoing [20]. Currently there are no standard approaches to treating CRPC-neuroendocrine cancers, which are associated with a mean 7-mo survival time. Several groups have now reported altered signaling pathways that may represent therapeutic target options. These include engagement of N-myc signaling and upregulation of aurora kinase A [23]—importantly, aurora kinase A is a *druggable* target, with clinical trials ongoing. Such studies may define the paradigm of bedside to bench to bedside medicine that can represent the hallmark of biomarker-driven therapy.

3.1.3 RCC—the VHL/hypoxia inducible factor pathway—RCCs represent a diverse collection of histological subtypes, each with specific subsets of underlying molecular alterations. Clear cell RCC (ccRCC), the most common and among the most aggressive histological variant, is highly associated with inactivation of the tumor suppressor *VHL* [24]. The *VHL* gene undergoes inactivation via point mutations, genomic deletions, and gene methylation in ccRCC. The VHL protein normally promotes ubiquitination and degradation of hypoxia inducible factors (HIFs) such as HIF1α and HIF2α, transcription factors that act as key regulators of the hypoxic response. Inactivation of VHL in RCC leads to increased HIFα expression, and increased activation of targets genes such as *VEGF* and *PDGF* [24].

Because of the universality of *VHL* inactivation and activation of the HIF/vascular endothelial growth factor (VEGF) pathways in RCC, interference with downstream effects of HIF (in particular *VEGF* and *PDGF* signaling) emerged as a major focus of drug development and clinical research over the past decade. Approved agents targeting these pathways include bevacizumab (Avastin), a humanized monoclonal antibody that binds VEGF, and orally active inhibitors targeting multiple tyrosine kinases and growth factor receptors (including VEGFR and PDGFR signaling)—these include sorafenib (Nexavar), sunitinib (Sutent), pazopanib (Votrient), and axitinib (Inlyta). The early trials employing bevacizumab demonstrated proof of principle in human patients that agents inhibiting VEGF signaling could significantly alter tumor progression in RCC [25,26]. Since then, antitumor activity of these agents has been well established in a series of phase 3 clinical trials, with

improvement in both progression-free and overall survival [27–31]. However, molecular predictors of response to these agents remain unclear. Alterations in the VHL-VEGF signaling axis do not perfectly correlate with response [32]. These agents also have activity in nonclear cell histologies of RCC, which classically do not display genomic alterations in these signaling pathways. Clearly, ongoing research has the potential to identify markers that may allow substratification of RCC patients to individualized treatment regimens.

3.1.4 RCC—mTOR Signaling—mTOR is an intracellular kinase that acts as a signaling node in the phosphoinositide 3-kinase (PI3-kinase)/Akt pathway, and functions to coordinate a number of cellular events surrounding growth and energy sensing and regulation, including regulation of protein translation, degradation, and signaling. Like VHL inactivation and upregulation of hypoxia transcriptional programs, activation of the mTOR/PI3K pathway is common in RCC [33]. Genomic alterations in this pathway are relatively uncommon when estimated from a single tumor sample, with mutations in genes such as *MTOR*, *TSC1*, *PIK3CA*, and *PTEN* occurring in less than 10% of RCC patients [34]. However, assessment of tumor heterogeneity in RCC and definition of tumor evolution using phylogenetic trees has helped reshape biological understanding and clinical implications of these findings. It is increasingly clear that somatic mutations in the mTOR pathway display clear evidence of intratumor heterogeneity, commonly occurring in some tumor subclones but not others. Somatic mutations in this pathway therefore occur later in tumor evolution than VHL and 3p loss of heterozygosity. Tumor sampling bias inherent to such intratumor heterogeneity hinders approaches to define activation of the mTOR pathway in order to guide therapy [35,36]. Inhibitors of mTOR signaling are currently used as standard options for poor risk RCC patients. Initial trials showed activity of temsirolimus in RCC, improving both PFS and OS compared with interferon-α [37,38]. Further analyses suggested activity in both ccRCC and other subtypes, and temsirolimus was subsequently approved for therapy of advanced RCC. The oral agent everolimus was shown to improve survival compared with placebo in patients with progressive disease *after* tyrosine kinase inhibitor therapy [39], and is currently being evaluated as an adjuvant therapy for patients at increased risk for progression following radical nephrectomy (NCT 01120249). These mTOR-directed therapies continue to be a mainstay of the armentarium in advanced RCC. In addition, mTOR inhibition has emerged as a standard therapy in renal angiomyolipoma [40,41], consistent with the critical role of the tuberous sclerosis complex-mTOR pathway in the pathogenesis of these lesions [42].

3.1.5 Targeted therapy—conclusions—In general, the targeted agents described above —in both prostate cancer and RCC examples—improve patient survival compared with prior generations of therapy, while at the same time displaying milder toxicity profiles. However, they do not represent curative therapies—complete responses are highly uncommon, and the survival advantages displayed are measured in months, not years. Additional studies and clinical trials are still needed to improve current practice and better understand predictors of response, sequencing of agents, and comparative efficacy of the current agents.

3.2 Predictors of response to standard of care therapies

The definition of biomarkers that can predict the success or failure of standard of care therapies is one of the most important areas of active research in urologic oncology. This has the potential for major impact on patients' lives by enriching treated patients for those likely to respond, improving the overall response rates for therapies with limited response rates overall (but dramatic response in a subset of patients), and allowing patients with a low likelihood of response to move on to other lines of treatment or to clinical trials.

3.2.1 Predictors of response to platinum chemotherapy in urothelial cancer—
Perhaps the most impressive recent example of this paradigm in urology is predictors of response to platinum chemotherapy in urothelial cancer. Level I evidence supports the utility of platinum-based chemotherapy regimens in the metastatic [43] and neoadjuvant settings [44,45]. In the neoadjuvant setting, methotrexate, vinblastine, Adriamycin, and cisplatin and other regimens have shown improved overall survival compared with radical cystectomy alone [44,45]. However, the absolute increase in overall survival is small (about 5% at 5 yr) based on meta-analyses [46–48], leading many to question the general application of the neoadjuvant approach to all patients with muscle invasive bladder cancer [49]. Importantly, patients who show complete response of the primary tumor (pT0N0 at cystectomy) appear to have the most major benefit in terms of overall survival.

It is clear that not all patients benefit from cisplatin-containing chemotherapy regimens, and morbidity is not trivial, but a minority of patients has a striking (and possibly curative) response. Therefore, defining the subset of patients and tumors likely to respond could have major impact [49]. Many studies in the past have examined candidate predictive biomarkers for cisplatin response—results have been mixed, and despite decades of research, no biomarkers to date have shown adequate predictive value to be currently utilized in the clinic [50]. However, the recent advent of next-generation technologies for unbiased, genome-wide molecular profiling of cancers has renewed hope for defining these biomarkers. Van Allen and colleagues [51] performed whole-exome sequencing on pretreatment muscle-invasive urothelial carcinoma from a defined set of patients with either a complete pathologic response/residual carcinoma in situ only or persistent muscle invasive cancer following cisplatin-based neoadjuvant chemotherapy. They identified somatic mutations in *ERCC2*, a component of the nucleotide excision repair system, as occurring preferentially in responders. Similarly, Plimack et al [52] showed that lesions in DNA repair genes *ATM*, *RB1*, and *FANCC* predicted pathologic response to neoadjuvant cisplatin. Others have reported alterations in genes affecting other DNA repair pathways as potentially important for prognosis, reinforcing this theme [53,54].

Other studies have revealed different potential biomarkers of response to platinum-based chemotherapy regimens. Utilizing targeted sequencing of urothelial carcinoma (muscle invasive and metastatic tumors) from patients treated with platinum-based chemotherapy regimens, Groenendijk and colleagues [55] reported that *ERBB2* mutations were associated with improved response to neoadjuvant chemotherapy. The Southwest Oncology Group has initiated an intergroup clinical trial to validate the COXEN algorithm as a predictive marker for response to neaodjuvant chemotherapy prior to radical cystectomy (NCT 02177695). If

validated, a phase 3 trial will be initiated to evaluate COXEN-directed neoadjuvant chemotherapy. Finally, distinct subtypes of bladder cancer have also been identified at the molecular level, including basal and luminal subtypes (similar to breast cancer) and a chemoresistant subtype with a distinct signature of p53 activation [56]. Heterogeneity at the level of tumor itself, stage of disease, patient characteristics, and treatment variability, complicate interpretation of these studies across cohorts, and necessitate extensive validation in well-annotated and more homogeneous patient cohorts. Further prospective data will be necessary to integrate all these findings, and most importantly, define the true clinical utility of any markers in practice.

3.2.2 CRPC and DNA repair in prostate cancer—A recent landmark study exposes the molecular underpinnings of CRPC and provides unprecedented insight to biology and mechanisms of therapy resistance in this disease. The SU2C/PCF Prostate Dream Team performed comprehensive molecular characterization of the metastatic tumors in 150 men with CRPC, revealing a high degree of actionable events, including frequent alterations in *AR* and *PI3K* signaling [10]. Furthermore, nearly 20% of CRPC samples harbored somatic genomic lesions in components of DNA repair pathways (such as *BRCA2*, *BRCA1*, and *ATM*). This is especially timely given the recent emergence of polyadenosine diphosphate ribose polymerase inhibitors as therapeutic options for patients with DNA repair deficient cancers. A phase 2 trial of the polyadenosine diphosphate ribose polymerase inihibitor olaparib in metastatic CRPC showed patient responses specifically associated with defects in DNA repair pathways [57], with further trials ongoing. Platinum agents are reported to have similar activity in this patient population [58]. Furthermore, emerging data also suggest that CRPC patients have a surprising prevalence of germline defects in DNA repair genes (eg, *BRCA* carriers), expanding the potential impact [59].

3.3 Immunotherapy

Urologic malignancies have a relatively long history of successful treatment with agents modulating the immune response to tumors. These include the standard of care use of bacillus Calmette-Guérin in urothelial cancer, and application of agents such as IL-2 and interferon in the armamentarium against RCC [60,61]. Interestingly, like many therapies, there appears to be specific subsets of patients with robust and often durable responses to these agents [62–64]. Newer approaches that have focused on the inhibition of immune checkpoint molecules that can restrict antitumor immune responses have also shown promise. Therapy targeting the cytotoxic T-lymphocyte-associated protein 4 T-cell checkpoint receptor (eg, ipilumimab) has shown some suggestion of response in prostate cancer clinical trials. In RCC, limited human trials have shown potentially impressive response rates using agents targeting the programmed cell death protein-1/programmed death-ligand 1 (PD-L1) interaction [65]. Both anticytotoxic T-lymphocyte-associated protein 4 and programmed cell death protein-1/PD-L1 therapy are under active investigation in urothelial carcinoma, with promising results [66]—perhaps most exciting, responses in patients are often early, durable, and associated with expression of targeted relevant biomarkers (eg, PD-L1). These studies focusing on immunotherapy in urologic malignancy have been extensively reviewed elsewhere; the potential to define predictive biomarkers for these classes of agents remains an active area of investigation [67,68]. These approaches

target the adaptive immune response and there are also other efforts targeting the innate immune response that may help develop better responses in nonresponders in combination with adaptive approaches.

3.4 Lessons from outlier responders

Exceptional responders—those patients whose cancers have an unusually robust and positive response to specific agents—can inform the biology of these diseases, highlight pathways for intervention, and define biomarkers for prediction of a therapeutic response. This approach has yielded results. In urothelial carcinoma, genome sequencing revealed that a patient with an exceptional response to everolimus harbored mutations in the *mTOR* and *NF* genes. These alterations were subsequently shown to impact the response of cancer cells to everolimus, nominating these alterations as potential biomarkers of response to *mTOR* inhibition [69]. Similarly, a patient with metastatic prostate cancer with exceptional response to cisplatin (after suggestion of small cell morphology) was shown to have inactivation of the *FANCA* gene, a key component of DNA repair pathways modulating response to platinum-based chemotherapeutics [70]. These reports, while anecdotal in nature, underscore the potential utility in gaining mechanistic insight and defining predictive markers from outlier responders. Such reports also highlight another challenge—given that rare subsets of patients may respond exceptionally well to therapies that may be ineffective in a population as a whole, how do we establish the definition of a *negative* clinical trial? In the absence of pre-existing genomic information, the *tails* of negative trials, consisting of the most robust responders in the population, may harbor informative information regarding predictive biomarkers.

This idea has real importance as the field of precision medicine evolves in urologic oncology. Many distinct, legitimately targetable alterations, with currently available therapeutics of proven efficacy, exist in urologic malignancies. However, they may be exceptionally rare, and occur in only a few percent of patients, and across different types of malignancies rather than enriched in one type. Furthermore, consideration should be given to the clonal structure of the tumor and when the targetable somatic alteration occurs during the course of tumor evolution [71]. Targetable somatic alterations occurring early on in tumor evolution, within the trunk of the tumor's evolutionary tree, present in every cancer cell, may provide more robust biomarkers of tumor response than alterations such as the mTOR pathway in ccRCC; however, these are subject to tumor sampling bias, usually occurring within a cancer subclone, present in some tumor regions but not others [72]. It should also be borne in mind that large-scale alterations in whole or parts of chromosomes that are currently refractory to contemporary targeted therapy strategies, can also drive tumor progression. For instance, in papillary renal cancer driver gene mutations are often subclonal alterations, in contrast to large-scale chromosomal alterations that were found to be clonal in nature [73].

Now that comprehensive molecular profiling is available on multiple urologic malignancies, through The Cancer Genome Atlas, International Cancer Genome Consortium, and other efforts, clear examples of rare but clinically important alterations are emerging. Amplifications, activating mutations, and gene fusions in the kinase *BRAF* (a common

driver in melanoma and other cancers) occur in roughly 1–5% of prostate cancers—these may be targetable with currently available inhibitors [10,74–76]. Amplifications and mutations in *ERRB2*, encoding the growth factor receptor tyrosine kinase HER2/neu, are present in about 10% of muscle invasive bladder cancers [77–79]—these cancers may be susceptible to trastuzumab (Herceptin). Mutations in the epigenetic modifying enzyme *IDH1*, one of the most common mutations in gliomas, occur in about 1% of prostate cancers [10,75]. *IDH1* mutation also represents an attractive target for therapy, with promising preclinical data [80]. These are just a few examples of alterations that have high promise as therapeutic targets, but are identified in only a small minority of patients. Highlighting the potential of this approach, the National Cancer Institute has embarked on the Exceptional Responders Initiative, a bedside to bench genomic approach to define the molecular underpinnings of rare but exceptional patient responses.

This raises an obvious concern: how can we possibly study a biomarker or target that occurs in only 1% of a given population? Understanding how to rigorously evaluate comparative treatment efficacy and patient responses in this new paradigm will be a critical challenge, given the limited number of patients with any one disease that may have the alterations of interest. One approach to this that has been suggested and now implemented is the idea of the *basket* trial—a novel form of clinical trial design that has emerged to meet the needs of the genomics era. The hypothesis underlying basket trials is that the molecular marker will predict tumor response to specific therapies across disease types. Such trials have generated considerable interest because they incorporate current information about genomics and precision medicine while promising the ability to identify favorable responses to targeted therapy with a relatively small number of patients. The National Cancer Institute Molecular Analysis for Therapy Choice trial is one prominent example of this approach. However, these come with their own unique limitations, including the need for prospectively collected, detailed (and expensive) molecular profiling data. In addition, the potential success of each basket trial is likely inextricably linked to the reliability of the target or marker in question and the specific therapy utilized. Unfortunately, not all therapies will *hit* the target in all cancer types, and not all cancers may respond the same way to effective blockade of all pathways. These complicating factors will likely continue force the evolution of clinical trial design.

4. Conclusions

Major advances have been made in cataloguing the genomic, transcriptomic, proteomic, and epigenetic alterations across urologic malignances. We have an improved understanding of the molecular mechanisms underlying these diseases, and therapies aiming to leverage this knowledge continue to emerge. Critical steps going forward will be to refine the list of truly predictive biomarkers and therapeutic targets, and evaluate their impact in real-world clinical settings. The continuing evolution of clinical trial design must proceed with this process, as evaluation of novel agents, with novel predictors will require novel approaches to define the population to be treated, and define efficacy in that population.

Acknowledgments

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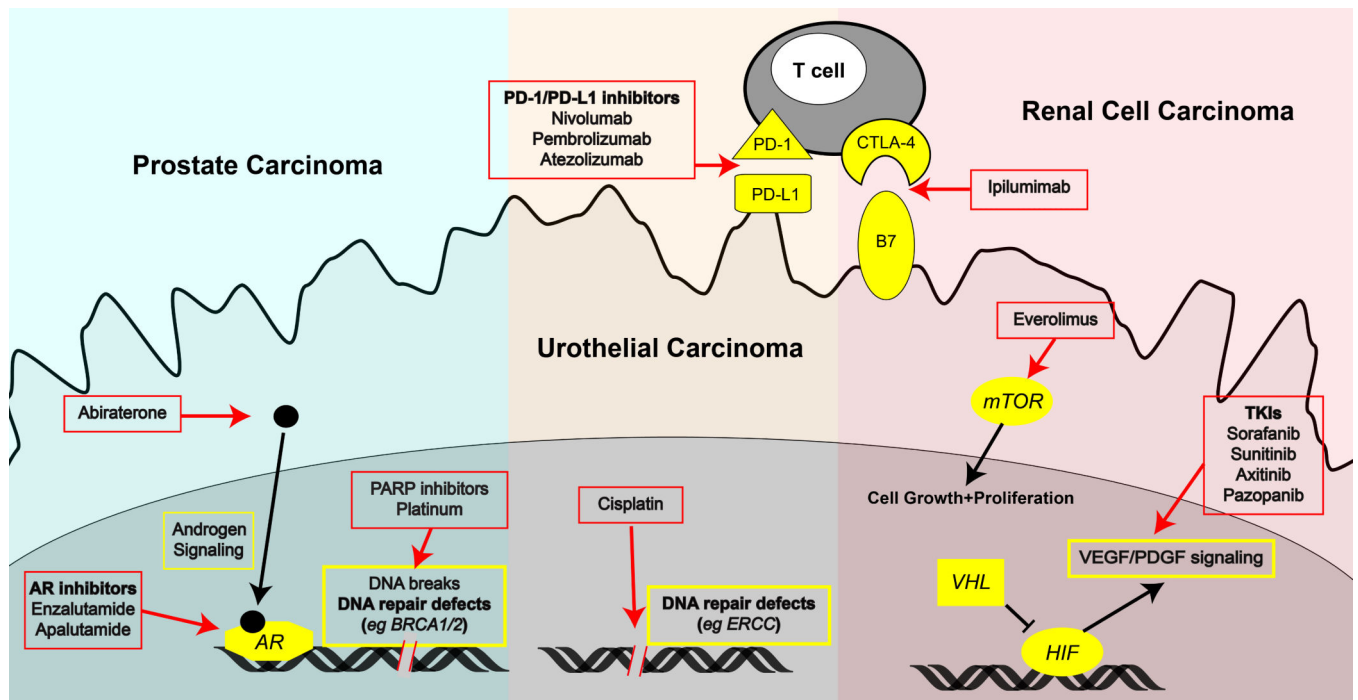
Fig. 1.

Landscape of precision urologic oncology. Relevant biological pathways, therapeutic targets, and therapies are highlighted for prostate cancer (left), urothelial cancer (center), and renal cell carcinoma (right). Therapeutics are outlined in red; biological pathways and targets are shown in yellow. Immunotherapy approaches using checkpoint inhibitors (top) may be applicable across disease histologies, with the most current evidence in renal and urothelial cancer. AR = androgen receptor; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; mTOR = mechanistic target of rapamycin; PD-1 = programmed cell death protein 1; PDGF = platelet-derived growth factor; PD-L1 = programmed death-ligand 1; TKIs = tyrosine kinase inhibitors; VEGF = vascular endothelial growth factor.

Table 1

Summary of potential biomarker directed therapy across urologic oncology

Prostate cancer			
Therapy	**Mechanism of action**	**Potential biomarkers**	**References**
AR-directed agents Enzalutamide Abiraterone Apalutamide	Inhibition of androgen receptor signaling	Androgen receptor mutations/amplifications AR-V7	Azad et al 2015 [14] Azad et al 2015 [15] Salvi et al 2015 [16] Li et al 2013 [17]
DNA damaging agents PARP inhibitors (olaparib) Platinum chemotherapy (cisplatin, carboplatin)	Induction of double strand DNA breaks	Defects in DNA repair genes—*BRCA1/2, ATM*	Robinson et al 2015 [10] Mateo et al 2015 [57] Cheng et al 2016 [58]
AURKA inhibitors	Aurora kinase inhibition	NEPC; AURKA upregulation; increased N-myc signaling	Beltran et al 2011 [23]
CTLA-4 inhibitor Ipilumimab	Antibody blocking the T-cell checkpoint receptor CTLA-4, resulting in improved immune surveillance		Kwon et al 2014 [81]

Urothelial carcinoma			
Therapy	**Mechanism of action**	**Potential biomarkers**	**References**
Platinum chemotherapy Cisplatin containing regimens: MVAC, GC	Induction of double strand DNA breaks (and other damage)	DNA repair defects: *ERCC2* mutations *ATM, RB, FANCC* alterations *ERBB2* mutations	Van Allen et al 2014 [51] Groenendijk et al 2015 [55] Plimack et al 2015 [52]
PD-1/PD-L1 inhibitors Nivolumab Pembrolizumab Atezolizumab	Targeting PD-1/PD-L1 interaction resulting in improved immune surveillance	PD-L1 High mutational load	Powles et al 2014 [66] Rosenberg et al 2016 [82]

Renal cell carcinoma			
Therapy	**Mechanism of action**	**Potential biomarkers**	**References**
Anti-VEGF Bevacizumab	Monoclonal antibody against VEGF	VEGF and VEGF related proteins	Escudier et al 2008 [83] Rini et al 2008 [84]
Tyrosine kinase inhibitors Sunitinib Sorafanib Pazopanib Axitinib	Inhibition of receptor tyrosine kinases downstream of VHL/HIF-1: VEGFR, PDGFR, etc.	VEGF and VEGF related proteins	Rini et al 2008 [84] Escudier et al 2009 [85]
mTOR inhibitors Temsirolimus Everolimus	Inhibition of mTOR	mTOR activity (P-S6)	Cho et al 2007 [86]
PD-1/PD-L1 inhibitors Nivolumab Pembrolizumab Atezolizumab	Targeting PD-1/PD-L1 interaction resulting in improved immune surveillance	PD-L1 High mutational load	Motzer et al 2015 [87] Taube et al 2014 [88]

AR = androgen receptor; AURKA = aurora kinase A; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; GC = gemcitabine and cisplatin; mTOR = mechanistic target of rapamycin; MVAC = methotrexate, vinblastine, doxorubicin, cisplatin; NEPC = neuroendocrine prostate cancer; PARP = polyadenosine diphosphate ribose polymerase; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; VEGF = vascular endothelial growth factor.