Summary from the First Kidney Cancer Research Summit, September 12-13, 2019: A Focus on Translational Research

Toni K. Choueiri, MD[1]*, Michael B. Atkins, MD[2], Ziad Bakouny, MD, MSc[1], Maria I. Carlo, MD[3], Charles G. Drake, MD, PhD[4], Eric Jonasch, MD[5], Payal Kapur, MD[6], Bryan Lewis, JD[7], W. Marston Linehan, MD[8], Michael J. Mitchell, PhD[9], Sumanta K. Pal, MD[10], Kevin Pels, PhD[1], Susan Poteat, MS[7], W. Kimryn Rathmell, MD, PhD[11], Brian I. Rini, MD[11], Sabina Signoretti, MD[1,12], Nizar Tannir, MD[5], Robert Uzzo, MD, FACS[13], Christopher G. Wood, MD, FACS[5], Hans J. Hammers, MD, PhD[6]

[1]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

[2]Georgetown Lombardi Comprehensive Cancer Center, Washington, DC

[3]Memorial Sloan Kettering Cancer Center, New York, NY

[4]Columbia University Medical Center, New York, NY

[5]University of Texas MD Anderson Cancer Center, Houston, TX

[6]University of Texas Southwestern Medical Center, Dallas, TX

[7]KidneyCAN, Philadelphia, PA

[8]National Cancer Institute, National Institutes of Health, Bethesda, MD

[9]Department of Bioengineering, University of Pennsylvania, Philadelphia, PA

[10]City of Hope Comprehensive Cancer Center, Duarte, CA

[11]Vanderbilt University Medical Center, Nashville, TN

[12]Brigham and Women's Hospital, Harvard Medical School, Boston, MA

[13]Fox Chase Cancer Center, Philadelphia, PA

*Correspondence to: Toni K. Choueiri, MD, Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, 450 Brookline Ave, Dana 1230, Boston, MA, 02115 (e-mail: toni_choueiri@dfci.harvard.edu)

Abbreviations:
BHD: Birt-Hogg-Dubé
CAR-T: chimeric antigen receptor T
ccRCC: clear cell renal cell carcinoma
cGAMP: cyclic guanine monophosphate-adenosine monophosphate
chRCC: chromophobe renal cell carcinoma
CIMP: CpG island methylated phenotype
EGFR: epidermal growth factor receptor
eHsp90: extracellular heat shock protein 90
GGT1: gamma-glutamyl transferase 1
HERV-E: human endogenous retrovirus type E
Hsp90: heat shock protein 90
ICI: immune checkpoint inhibitor
IHC: immunohistochemistry
IO: immuno-oncology
irRECIST: immune-related response evaluation criteria in solid tumors
KCRP: Kidney Cancer Research Program
KCRS: Kidney Cancer Research Summit
MMP: matrix metalloprotease
mtDNA: mitochondrial DNA
nccRCC: non-clear cell renal cell carcinoma
NIH: National Institutes of Health
NSCLC: non-small cell lung cancer
ORR: objective response rate
OS: overall survival
PARP: poly(ADP-ribose) polymerase
PFS: progression-free survival
pRCC: papillary renal cell carcinoma
RCC: renal cell carcinoma
RECIST: response evaluation criteria in solid tumors
RMC: renal medullary carcinoma
scRNA-seq: single cell RNA-sequencing
SPORE: Specialized Programs of Research Excellence
TCGA: The Cancer Genome Atlas
T_{eff}: T-effector cell
TKI: tyrosine kinase inhibitor
TME: tumor microenvironment
tRCC: translocation renal cell carcinoma
VEGF: vascular endothelial growth factor
VOC: volatile organic compound
WES: whole exome sequencing

Abstract

Kidney cancer is one of the ten most common cancers both in the United States and worldwide. Until this year, there had not previously been a conference focused on translational studies in the broad and heterogeneous group of kidney cancers. Therefore, a group of researchers, clinicians, and patient advocates dedicated to renal cell carcinoma (RCC) launched the Kidney Cancer Research Summit (KCRS) to spur collaboration and further therapeutic advances in these tumors. This commentary aims to summarize the oral presentations and serve as a record for future iterations of this meeting. The KCRS sessions addressed the tumor microenvironment, novel methods of drug delivery, single cell sequencing strategies, novel immune checkpoint blockade and cellular therapies, predictive biomarkers and rare variants of kidney cancers. In addition, the meeting included 2 sessions to promote scientific mentoring and kidney cancer research collaborations. A subsequent KCRS will be planned for the fall of 2020

The inaugural Kidney Cancer Research Summit (KCRS) was held September 12-13th, 2019 in Philadelphia, Pennsylvania. This meeting was sponsored by KidneyCAN, a grassroots movement formed to support patient advocacy and accelerate kidney cancer research, and based largely on projects funded through the Kidney Cancer Research Program (KCRP), an allocation of $10 million from the Department of Defense's Congressionally Directed Medical Research Programs in 2017 to address challenges and controversies facing the kidney cancer field (Figure 1). Importantly, many basic and translational researchers funded by KCRP lack opportunities to regularly interface with clinicians that could benefit from and help develop their research. KCRS brought these parties together with the goal of advancing the standard of care in renal cell carcinoma (RCC) through facilitating collaboration and communication in an intimate scholarly setting (Figure 2). The unique small meeting format consisted of short talks followed by question and answer sessions, as well as a mentoring panel and moderated open discussions (Table 1).

Thinking Outside the Tumor

The first session focused on molecular features of tumor cells and other cells in the tumor microenvironment (TME) that could be valid therapeutic targets in the future. For instance, upregulation of the kidney-specific transcription factor FoxD1 is inversely correlated with patient survival and increased fibrosis in clear cell renal cell carcinoma (ccRCC) tumors. To determine if stromal fibroblasts are a therapeutic target, Leif Oxburgh's group is using patient tissue samples to develop a synthetic ccRCC tumor model that recapitulates stromal involvement. They will use this model to study the impact of fibroblasts on tumor structure and stiffness, secreted factors, and immune involvement[1].

Many tumors overexpress the enzyme poly(ADP-ribose) polymerase (PARP) to repair single-strand DNA breaks, and trials of PARP inhibitors like olaparib in RCC are ongoing. Olaparib and other clinical PARP inhibitors block PARP's NAD^+-binding site, but these compounds have off-target effects at other NAD^+-binding proteins[2]. Vladimir Kolenko and colleagues developed a novel class of compounds

that block PARP from binding to histones, a strategy which should yield greater selectivity for PARP. They now intend to optimize the activity, pharmacokinetics, and safety of these molecules via an iterative, structure-guided approach[3].

Tumors secrete matrix metalloprotease (MMP) enzymes to degrade the extracellular matrix and promote tumor invasion. MMP2 expression is associated with poorer outcomes in RCC, but therapies targeting MMP2 have thus far been unsuccessful. Dimitra Bourboulia's group has identified a small molecule that blocks the kinase c-Abl from phosphorylating MMP2, which prevents its stabilizing interaction with extracellular heat shock protein 90 (eHsp90) and reduces MMP2 enzymatic activity in vitro. Her group is looking at potential therapeutic combinations targeted at the c-Abl/eHsp90/MMP2 axis that minimize tumor invasiveness.

The third most commonly mutated gene in RCC, *SETD2*, encodes a tumor suppressor that trimethylates both histone H3K36 and tubulin[4]. Laura Banaszynski's group found that overexpression of SETD2 in ccRCC cell lines decreased tumor cell migration but curiously enhanced their proliferation as well. Since SETD2 uses the metabolite S-adenosyl methionine as a methyl donor, they are investigating broader metabolic dysregulation caused by *SETD2* mutations in ccRCC, and whether there are opportunities for synthetic lethality with other metabolic targets.

Monoallelic loss and/or certain mutations prohibit SETD2 from methylating tubulin, leading to defects in mitosis but not histone regulation[5,6]. While SETD2's role in histone methylation has been studied in greater detail, Durga Tripathi's group is trying to identify "readers" and "editors" of methylation and other post-translational modifications on tubulin, and explore the relationship between mitotic defects and the inflammatory status of RCC tumors.

This session featured basic scientists translating their research into the kidney cancer setting, and clinicians lent their perspectives. Oxburgh and Bourboulia proposed targeting the TME to overcome

its immunosuppressive features and reduce metastatic potential. The audience was excited that Kolenko's research could expand the largely underinvestigated strategy of PARP inhibition (monotherapy and combinations) in RCC[7]. Banaszynski and Tripathi pointed to the consequences of *SETD2* mutation in key cellular pathways, which could influence RCC treatment strategies in the future.

Novel Methods of Drug Delivery

This session focused on various vectors for maximizing drug exposure at the tumor site. Drug-loaded nanoparticles or alternative materials targeted to the tumor, TME, or immune cells are potential delivery vectors for optimizing efficacy and reducing the toxicity of infused immuno-oncology (IO) drugs[8]. Michael Mitchell's research focus is engineering nucleic acid-loaded nanoparticles[9] targeted to immune cells in lymph nodes, for example, to increase expression of tumor-associated antigens and enhance the antitumor immune response[10].

Nanoparticles accumulate in tumors because of phagocytosis by tumor-associated macrophages[11]. Paula Bates is interested in how nanoparticles intrinsically repolarize macrophages from the immunosuppressive M2 to immunostimulatory M1 state, as has been demonstrated with nanoparticle drugs like iron oxide and nab-paclitaxel[12,13]. Her group is screening these and other FDA-approved nanoparticle drugs for macrophage repolarization in cell lines and animal models, with the further goal of identifying those that synergize with anti-PD-1 therapy in vivo.

Adenosine has anti-inflammatory and immune inhibitory functions, and is elevated in RCC patients who do not respond to anti PD-1 therapy. Wilson Meng showed that intratumoral injection of a hydrogel[14] containing anti-PD-L1 antibody and adenosine deaminase only modestly reduced tumor burden in PD-1 resistant RENCA murine model of RCC, but demonstrated promising immune stimulatory effects, including increases in draining lymph node size and markers of tumor inflammation. Their current studies involve computational modeling of drug bioavailability to optimize dosing.

Without a delivery vehicle, the STING agonist cyclic guanosine monophosphate-adenosine monophosphate (cGAMP) exhibits poor pharmacokinetic properties and cannot enter cells. John Wilson's group designed pH-responsive cGAMP nanoparticles that induce $CD8^+$ and $CD4^+$ T cell tumor infiltration in RENCA mice. Their ongoing investigations test for antitumor effects in this in vivo model using either single-agent cGAMP nanoparticles or combined with anti-PD-L1 antibodies.

These talks shifted the focus towards the clinical setting, especially the proposed use of nanoparticles to augment molecules with poor solubility and/or membrane penetrance. Notably, each of these researchers is focused on invigorating immune response in vivo, but RENCA mice poorly recapitulate metastatic RCC in humans[15]. Therefore, there was a general consensus that more accurate murine models are needed for preclinical development of these drug delivery strategies.

Single Cell Sequencing Strategies

Single cell RNA sequencing (scRNA-seq) is a novel technique for characterizing tumor heterogeneity to dissect and understand the TME. A pilot study used scRNA-seq to identify cell type of origin for certain histologies of renal tumors[16]. Ari Hakimi explained that 'diffusion mapping' can show how cells transition between different states in response to therapy. While preliminary data are encouraging, batch correction will be needed to enable comparison of tumor samples across multiple patients[17]. Another limitation of scRNA-seq is that fresh tissue is required; however, emerging methods (such as isolating and sequencing RNA from cell nuclei[18]) can use banked frozen tissue to expand the pool of sequenceable material.

Most cells contain hundreds or thousands of mitochondria that each have multiple copies of their own genome. The presence of mutated and/or aberrant mitochondrial DNA (mtDNA) in each cell, quantified as 'heteroplasmy', is a common phenomenon in cancer[19]. Heteroplasmy varies across RCC histologies, with the highest seen in papillary RCC (pRCC) and ccRCC the lowest[20]. Ed Reznik is optimizing

a new scRNA-seq method that detects mtDNA mutations and analyzes their impacts on tumor metabolism.

Immune infiltration, especially $CD8^+$ T cells, increases during kidney cancer progression. David Braun showed how scRNA-seq can identify distinct immune cell states of activation or exhaustion, which could aid in understanding the mechanisms underlying response and resistance to immune checkpoint inhibitor (ICI) therapy. His research further integrates bulk genomic, transcriptomic, and immunohistochemistry (IHC) data with single cell T cell receptor (TCR) sequencing to identify the antigen specificity of tumor-infiltrating T cells[21]. He is now performing scRNA-seq at multiple timepoints during therapy to unravel the molecular features and regulatory networks of tumor and immune cells.

The audience was excited about the potential of using scRNA-seq to elucidate the determinants of response and resistance to RCC therapies, and to better understand the heterogeneous TME in RCC. However, key challenges such as sample availability, difficulty with sample processing, and prohibitive costs were highlighted as important limitations to overcome.

American Urologic Association Scientific Mentoring Session

This session featured preliminary research from early career investigators. Philip Abbosh hypothesizes that *SETD2* loss may impact the biology of response to immunotherapy. He is investigating whether mutations in *PBRM1* and *SETD2* are associated with an exhausted T cell gene signature in localized RCC, and their potential as biomarkers of outcomes with ICIs. Ken Batai's project serves Native Americans and Hispanic Americans, minority populations that are well-represented in his region and who exhibit increased mortality from RCC and higher incidences of early-onset RCC[22]. He seeks to identify risk factors such as obesity, and uses whole transcriptome and whole exome sequencing (WES), as well as profiling epigenetic and metabolomic profiling to determine a biological mechanism for early-onset RCC. Brandon Manley aims to understand recurrent splice variants of the epidermal growth factor

receptor (EGFR) in ccRCC that lack the EGF-binding domain. He showed that localized ccRCC tumors expressing this EGFR variant are associated with decreased recurrence-free survival, and his research will attempt to define the function of the truncated receptor and validate its association with increased resistance to ICIs. Vivek Narayan proposes to monitor volatile organic compounds (VOCs) that are specific to malignant RCC cells, and has already tested a prototype sensor array that detected VOCs from ovarian cancer samples. He will now attempt to determine a VOC signature for RCC by screening against a larger cohort of benign control, localized, and metastatic RCC tumors, with the goal of creating a device that can assist with pre-surgical clinical staging and post-nephrectomy surveillance.

Novel Checkpoint Inhibitors and Cellular Immunotherapy

Immunotherapy targeting PD-(L)1 & CTLA-4 has greatly augmented the therapeutic landscape for RCC, and many researchers are on the hunt for other targets to further unleash the immune system against kidney tumors. The immune checkpoint protein VISTA is expressed on T cells, myeloid cells, and RCC tumor cells, but its receptor is currently unconfirmed[23]. Kathleen Mahoney is investigating whether VSIG3 or the negatively charged PSGL-1[24] is a binding partner for VISTA's histidine-rich, positively charged IgV domain, and testing antibodies blocking either of these interactions with VISTA for antiproliferative and cytotoxic effects in vitro and in the RENCA model.

HHLA2 is an immune checkpoint expressed on 47% of PD-L1$^-$ non-small cell lung cancers (NSCLC), potentially representing an immunotherapy target in patients that do not respond to PD-L1 blockade[25]. HHLA2 is also present in 80% of RCC and Rupal Bhatt, in collaboration with Gordon Freeman and colleagues, found PD-L1 expression to be non-overlapping with HHLA2 in RCC as well. HHLA2 can inhibit or stimulate immune function depending on whether it binds to ITIM or TMIGD2, respectively, so Bhatt's group has generated antibodies that selectively block the immunosuppressive HHLA2-ITIM interaction. Now they are studying HHLA2 regulation in vitro and in patient tumor samples, with the goal of advancing HHLA2-targeted therapies towards clinical development.

B7-H3 is overexpressed across RCC types, but this checkpoint is also present at very low levels in some normal tissues as evidenced by weakly positive IHC staining of stomach, adrenal & salivary glands, as well as activated bone marrow-derived dendritic cells. Hongwei Du demonstrated that these normal tissues escape cytotoxicity from B7-H3 targeted chimeric antigen receptor T- (CAR-T) cells, as treated mice did not suffer immune-related toxicities or tissue damage[26]. Moreover, anti-B7-H3 CAR-T cells were effective both in kidney cancer cell lines and in a mouse xenograft model of ccRCC. Based on these promising results, Du's team is advancing anti-B7-H3 CAR-T therapy to clinical trials in solid tumors.

PD-1/PD-L1 determination by IHC is limited by both the requirement of a tumor biopsy and the sampling bias involved in selecting a biopsy site for analysis. David Leung reports on the development of immunoPET imaging (first demonstrated in NSCLC[27]) to determine the immune checkpoint expression of each tumor, which correlates with PD-1/PD-L1 status as determined by IHC and response to immunotherapy. Testing in patients has produced no adverse effects to date; however, this technology cannot determine the PD-L1 expression status of primary kidney tumors because the imaging agent undergoes renal excretion. While Leung's team is primarily focused on PD-1/PD-L1 imaging, he also reported efforts by others to develop imaging agents for CD8, T cell activation, and CTLA-4[28–30].

In a fascinating case series described almost 20 years ago, patients with metastatic ccRCC received an hematopoietic stem cell transplant at the National Institutes of Health (NIH) that produced graft-versus-tumor responses resulting in prolonged remission for some patients[31]. A $CD8^+$ T cell clone isolated from one responding patient was found to recognize a tumor antigen encoded by human endogenous retrovirus type E (HERV-E) that is silenced in healthy tissue, but expressed in most cases of ccRCC[32]. Subsequently, the HERV-E reactive TCR was cloned for transduction into T cells that acquire selective killing of ccRCC cells. Rosa Nadal, who described this work, is leading a collaboration between the NIH and Loyola University testing the safety and efficacy of escalating doses of autologous HERV-E TCR transduced T cells in a phase I trial for patients with metastatic ccRCC. To make this therapy more

widely applicable, these collaborators are also developing HERV-E reactive CAR-T cells and TCRs targeting HERV-E antigens presented in more common HLA alleles[33].

Previous attempts to therapeutically target the cell surface receptor CAIX, which is widely expressed on ccRCC cells, have been unsuccessful. The chimeric antibody girentuximab did not show efficacy in high-risk RCC patients in a phase III clinical trial[34]; likewise, a phase I/II study of anti-CAIX CAR-T was halted for high grade hepatotoxicity resulting from CAIX expression on bile ducts[35]. Wayne Marasco's group has designed a CAR-T construct that simultaneously targets both CAIX and CD70, another RCC-specific epitope that is not expressed on bile duct tissue[36]. By changing the TCR costimulatory domain and using both $CD4^+$ and $CD8^+$ T cells, their optimized construct has increased antitumor activity and duration of response. They are currently testing this bispecific CAR-T therapy in patient-derived 3-D cell culture models of ccRCC.

While checkpoint inhibitors are now the front-line standard of care, a majority of patients will fail to respond; hence, the sustained interest in therapies targeting other putative immune checkpoints. This was another session where the lack of robust murine models was acknowledged. The audience overall was excited about immunoPET imaging, and pathologists present agreed that it will be a necessary improvement over IHC pathology review. Regarding T-cell and CAR-T therapies, it was felt that these will not be front-line therapies, and their development should be focused on advanced stage tumors.

Predictive Biomarkers

With the expanding armamentarium of cancer therapies for RCC, clinicians are hindered by a lack of validated predictive biomarkers for selecting the proper therapy in each patient. The phase III CheckMate-025 trial previously demonstrated an overall survival (OS) benefit for nivolumab over everolimus in patients with metastatic ccRCC who received prior anti-angiogenic therapy[37]. Toni

Choueiri and colleagues and another group both published independent studies suggesting that chromatin modifier mutations, particularly *PBRM1* truncating mutations, correlate with response to ICIs[38,39]. Choueiri's team validated these findings in the CheckMate-025 cohort, where *PBRM1* truncating mutations were associated with improved responses to nivolumab but not everolimus[40], suggesting *PBRM1*'s potential as a predictive (rather than prognostic) correlate of response to ICI. They will continue to evaluate other correlates of response to nivolumab and/or everolimus through integrative genomic and transcriptomic analyses.

Immune-related response evaluation criteria in solid tumors (irRECIST) is a modification of RECIST that captures atypical responders to immunotherapy, including PD-(L)1 inhibitors. Using irRECIST, Sabina Signoretti and colleagues reanalyzed progression-free survival (PFS) and objective response rate (ORR) results in the CheckMate-010 trial, a randomized phase II dosing study of nivolumab in patients with metastatic ccRCC. They showed that irPFS (5.5 months) was statistically significantly longer than PFS (3.3 months), and that tumor expression of PD-L1 by IHC was associated with irPFS but not PFS. Signoretti's team developed a combined biomarker model of response to nivolumab that identifies 3 groups of patients with distinct irPFS/irORR outcomes[41], and they are now validating this model in other prospective trials.

Various cytokines and angiogenic factors have been proposed as predictive biomarkers for response to vascular endothelial growth factor (VEGF) inhibitors, but many remain to be validated in studies containing both the intervention and control groups. Maxine Sun discussed results from the IMmotion150 randomized phase II study of atezolizumab (alone or combined with bevacizumab) versus sunitinib as first-line therapy for patients with metastatic RCC, wherein patients with gene expression signatures depleted for angiogenesis but enriched for T-effector cells (T_{eff}) and myeloid cells demonstrated statistically significantly longer PFS when treated with combination

atezolizumab/bevacizumab over sunitinib[42]. Unlike in CheckMate-025, *PBRM1* mutations in these treatment-naïve patients did not predict response to ICIs.

The goal of predictive biomarkers is to match patients with a specific therapy that is most likely to provide maximal efficacy and minimal toxicity, but an alternative approach is to give patients a combination of the best available therapies to increase likelihood of a response. Brian Rini presented an analysis of the IMmotion151 trial[43] that supports using the gene signatures developed from IMmotion150 (presented by Sun) to assign patients to combination VEGF-targeted tyrosine kinase inhibitor (TKI)+IO (angiogenesis high/T_{eff} high), TKI or TKI+IO (angiogenesis high/T_{eff} low), IO or IO+IO (angiogenesis low/T_{eff} high), or other agents (angiogenesis low/T_{eff} low). He suggested that other gene signatures (such as proliferation and metabolism) may identify other treatment subgroups, but ended by noting that RCC still lacks a 'real' clinical or genomic biomarker for or against any currently available therapy or combination.

The JAVELIN Renal 101 phase III randomized controlled trial of avelumab + axitinib showed improved PFS and ORR compared to sunitinib in treatment-naïve patients with advanced ccRCC[44]. Demonstrating the ability of the pharmaceutical industry to generate molecular datasets at scale and collaborate with an academic center to analyze and interpret those data, Paul Robbins presented a correlative analysis of this study that derived a 26 immune-related gene signature from RNA-seq of baseline tumor samples from each patient[45]. This signature, which was validated in an independent dataset, was associated with improved PFS exclusively in the avelumab + axitinib arm. Specific mutations and polymorphisms in *CD163L1*, *DNMT1*, and *PTEN* differentially correlated with outcomes, suggesting that they could constitute a combined biomarker for this combination. Robbins argued that academia-industry partnerships are an excellent opportunity to maximize the value of patient data from large trials.

The general discussion on this session focused on the frustrations with candidate biomarkers that are currently insufficient for optimizing patient selection. Despite *PBRM1* mutations being associated with benefit from ICI monotherapy, this has only been validated beyond first-line therapy. As immunotherapy-based combinations are now being increasingly used in the first-line treatment of RCC (with less of a role for subsequent line ICI monotherapy), all attendees agreed that the role of *PBRM1* mutations and other potential biomarkers will need to be comprehensively reassessed. Changes to the TME as a result of VEGF-TKI therapy may impact response to ICIs, which could also explain the synergy of combination therapy, but the dynamics of that change are currently unclear. Until our understanding of this biology improves, many clinicians will choose among active therapeutic regimens by avoiding toxicities.

Collaborations in Kidney Cancer Research

The KCRP sponsors kidney cancer research with the goals of increasing our understanding of tumor biology, improving patient care, and growing the field to increase collaboration both within and between institutions. Theresa Miller described KCRP funding mechanisms that support research at various stages of development: the Concept Award for early-stage innovative ideas; the Idea Development Award for emerging research programs supported by preliminary data; and the Translational Research Partnership Award to accelerate the most promising findings towards clinical utility. Additionally, the KCRP supports career development through its Academy of Kidney Cancer Investigators, and clinical-stage collaborations through its Clinical Consortium Award.

As recipient of the KCRP's 2017 Consortium Development Award, Eric Jonasch reported his progress in creating an interinstitutional platform for cultivating innovative early phase (I-II) clinical trials. Michael Jewett is launching a task force to study small renal masses, overdiagnosis of which leads to unnecessary treatment. James Brugarolas and Toni Choueiri described their Specialized Programs of

Research Excellence (SPORE) in RCC, centered at the University of Texas Southwestern Medical Center and the Dana-Farber/Harvard Cancer Center, respectively. Finally, Christopher Wood announced the Young Investigator and Advanced Discovery award recipients from the Kidney Cancer Association.

Translational Variants in Rare Kidney Cancers

Non-clear cell RCC (nccRCC) tumors are often lumped together despite their histological heterogeneity, variable molecular characteristics, and divergent clinical courses, but recent research is revealing the molecular drivers within discrete histologies. Drug development for nccRCC is driven by what works in ccRCC: trials comparing everolimus and sunitinib in metastatic nccRCC modestly favored sunitinib but yielded largely disappointing results[46,47]. James Hsieh described results from the recent KEYNOTE-427 trial in nccRCC showing more promising antitumor activity for first-line pembrolizumab monotherapy, with an ORR of 25%[48]. Response rates varied by RCC subtype, with the highest rate in unclassified RCC and the lowest in chromophobe (chRCC). A key challenge going forward will be correctly diagnosing RCC subtypes and matching them with effective therapies.

Mutations of the tumor suppressor gene *FLCN* are associated with Birt-Hogg-Dubé (BHD) syndrome, a hereditary condition characterized by benign fibrofolliculomas and certain renal tumors[49]. Mehdi Mollapour's team previously showed that the stability and function of FLCN depends on interactions with Hsp90 and its co-chaperones FNIP1/2[50]. Approximately 93% of all pathogenic *FLCN* mutations are truncating, and most appear to disrupt the stability of FLCN in vitro. These truncating mutations disrupt FLCN's interaction with FNIP1/2 and Hsp90, and the loss of these stabilizing interactions appears to be responsible for the pathogenicity of *FLCN* mutants. Mollapour is now investigating the biological functions of FLCN to identify new therapeutic targets in BHD-driven renal tumors.

Abnormal mitochondria, a low number of driver mutations, and alteration or loss of chromosomes 1, 2,6, 10, 13, and 17 distinguish chromophobe from other forms of RCC[51]. Elizabeth Henske showed that these tumors also exhibit decreases in certain metabolites, specifically 5-oxoproline and gamma-glutamyl amino acids. Her group connected these findings with data from The Cancer Genome Atlas (TCGA) demonstrating decreased expression of gamma-glutamyl transferase 1 (GGT1) in chRCC but not ccRCC or normal kidney tissue. Loss of GGT1 causes deficiency in glutathione salvage, so chRCC tumors overexpress other enzymes in this pathway and upregulate de novo glutathione synthesis[52]. Henske's team is currently developing additional cell lines and animal models to refine their model of chRCC pathogenesis and further investigate their sensitivity to oxidative stress and inhibitors of de novo glutathione synthesis.

Renal medullary carcinoma (RMC) is a very rare kidney tumor that almost exclusively occurs in the setting of sickle cell hemoglobinopathies, and typically manifests in the third decade of life[53]. Most RMC patients present with metastatic disease in the lymph nodes, lungs, liver, and/or bone, and median survival is just 13 months. RMC is defined by loss of SMARCB1, a subunit of the SWI/SNF chromatin remodeling complex, but there are currently no therapies specifically directed at SWI/SNF subunit defects. Pavlos Msaouel explained that the *SMARCB1* gene locus is particularly susceptible to deletions and translocations, which are pathologically compounded by medullary cells' impaired ability to repair DNA double strand breaks owing to the hypoxic and hypertonic nature of medullary tissue required for its role in concentrating urine[54]. Msaouel's goal is to develop mouse models to understand RMC pathogenesis and develop targeted therapies for this disease.

Translocation RCC (tRCC) tumors are defined by nuclear expression of *TFE3* gene fusions caused by chromosomal rearrangements that can involve multiple fusion gene partners, with 17 identified thus far. Roberto Pili's group developed patient-derived xenograft models of tRCC and determined that the PI3K/AKT/mTOR axis was a major downstream SFPQ-TFE3 fusion target[55]. Other groups have identified

additional pathway alterations resulting from other fusion partners[56]. Using a novel fluorescence resonance energy transfer-based assay, Pili showed that oncogenic TFE3 fusion proteins dimerize with wildtype TFE3 in the nucleus, and his group is now screening for small molecules that inhibit this dimerization, potentially disrupting the molecular processes underlying tRCC.

Papillary RCC can be driven by multiple distinct mutations as determined by TCGA data[57]. As the largest subtype of nccRCC, pRCC tumors are conventionally classified into types I & II, despite the poor reproducibility of these histologic classifications and the existence of other molecularly-derived subgroups. A particularly lethal form called CpG island methylated phenotype (CIMP) is driven by germline alterations to *FH* compounded by other mutations. Brian Shuch's group is testing the hypothesis that oncometabolites drive genetic instability and "BRCAness" in *FH*-deficient CIMP tumors, and they may therefore be sensitive to PARP inhibitors. To overcome limited responses to monotherapy, investigation of optimal therapeutic combinations in pRCC is ongoing.

Despite advances in our understanding of the molecular drivers of various RCC histologies, many rarer forms of nccRCC histologies remain poorly molecularly defined and effective therapeutic strategies are still beyond our reach. The general conclusion of the attendees was that a two-pronged approach will need to be pursued to improve the outcomes of patients with these tumors: first, multi-center clinical trials are needed to enroll enough patients to study interventions in rarer forms of nccRCC. These trials could attempt to evaluate therapies targeting specific nccRCC molecular alterations, such as with the ongoing PAPMET trial (NCT02761057) or ICI-based therapies that have already been shown to improve outcomes in ccRCC. Second, more concerted efforts are needed to better elucidate the molecular underpinnings of rare nccRCC subtypes. In the longer term, this could lead to the development of therapeutic strategies tailored for these tumors. Crucially, these efforts should also inform whether conventional histological or molecular classifications are more therapeutically relevant going forward, as is currently ongoing in pRCC.

Conclusion

The first annual KCRS meeting reflected both the immense strides that have been made in the treatment of RCC as well as the major challenges the field still faces. Academic scientists presented ideas that merged their own basic research into new therapeutic applications in ccRCC enabled by an evolving understanding of exploitable molecular alterations in kidney cancer, especially DNA repair pathways and epigenetic factors. Progress has also been made in rare kidney cancers, where researchers are discovering the genetic basis of highly pathogenic alterations and identifying targets for the drug development in diseases that currently lack any standard of care. Building on the burgeoning success of ICIs in unleashing the patient's immune system against the tumor, other researchers are inventing new drug delivery vectors that enhance efficacy and decrease the toxicity associated with current immunotherapies. Single cell sequencing promises to enhance our understanding of the various types and states of tumor and immune cells within the heterogeneous RCC microenvironment, and could aid in the ongoing search for robust biomarkers of response to targeted therapy and/or immunotherapy. Intra- and inter-institutional collaborations undergird many of the projects that were presented, reflecting how advances in RCC therapy are enabled by cooperation between academic centers, foundations, industry, patient advocates, and government agencies. Other challenges were not addressed in this meeting, many of which will be covered in the next summit in 2020 (Table 1). These topics include the availability of RCC cell line and murine models, emerging therapies targeting cellular processes upstream of VEGF, and improving therapeutic options for variant RCC tumors.

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Table 1. KCRS agenda by session.

Sessions	Topic	Presenters
Thinking Outside the Tumor	Moderated by Eric Jonasch and Sumanta K. Pal	
	Modeling the Effects of Stroma on Clear Cell Renal Cell Carcinoma	Leif Oxburgh
	Histone-dependent PARP-1 Inhibitors: A Novel Therapeutic Modality for the Treatment of Renal Cell Carcinoma	Vladimir Kolenko
	Kinase Signaling and Extracellular Matrix Proteolysis in Kidney Cancer	Dimitra Bourboulia
	Chromatin Dysregulation and Metabolism in Clear Cell Renal Cell Carcinoma	Laura Banaszynski
	Reading the SETD2 Methyl Mark on Microtubules	Durga N. Tripathi
Novel Methods of Drug Delivery	Moderated by Robert G. Uzzo and Michael J. Mitchell	
	Overcoming Biological Barriers to Cancer Immunotherapy Using Drug Delivery	Michael J. Mitchell
	Combining Immunotherapy with Nanoparticles for Improved Kidney Cancer Outcomes	Paula J. Bates
	Hydrogel-enabled Intratumoral Delivery of Anti-PD-1 Antibody and Adenosine Deaminase	Wilson Meng
	Reinvigorating Antitumor Immunity in Renal Cell Carcinoma with Nanoparticulate STING Agonists	John T. Wilson
Single Cell Sequencing Strategies	Moderated by Payal Kapur and Sabina Signoretti	
	Single Cell Sequencing	A. Ari Hakimi
	Architecture and Function of Mitochondrial DNA Mutations in Renal Cell Carcinoma	Ed Reznik
	Single-cell Transcriptomics to Understand the Drivers of Immune Checkpoint Inhibitor Response in RCC	David A. Braun
American Urologic Association Scientific Mentoring Session	With mentors Brian I. Rini, Robert G. Uzzo, Brian Shuch, Alexander Kutikov, Eric A. Singer, and Gennady Bratslavsky	
	Driver Mutations, Immune Microenvironment, and Response to Immune Checkpoint Blockade in Clear Cell Renal Cell Carcinoma	Philip H. Abbosh
	Integrative Approach to Understand Early-onset Clear Cell Renal Cell Carcinoma in Racially/Ethnically Diverse Patient Populations	Ken Batai
	Investigation of Aberrant EGFR Splice Variants in Clear Cell Renal Cell Carcinoma	Brandon Manley
	Novel Approach to RCC Early Diagnosis and Therapeutic Monitoring using Volatile Organic Compounds	Vivek K. Narayan
Novel Checkpoint Inhibitors and Cellular Immunotherapy	Moderated by Hans J. Hammers and Charles G. Drake	
	Is VISTA an Actionable Immune Checkpoint in Kidney Cancer?	Kathleen M. Mahoney
	Identification of a New Immune Checkpoint Pathway in RCC	Rupal S. Bhatt
	Targeting B7-H3 in Renal Cell Carcinoma via CAR-T Cells	Hongwei Du
	Development and Potentials for ImmunoPET Imaging	David K. Leung
	HERV-E TCR Transduced Autologous T Cells for Patients with Clear Cell	Rosa Nadal

	RCC	
	Design of Dual Targeted CAR-T Cells to Improve RCC Treatment Safety	Wayne A. Marasco
Predictive Biomarkers	Moderated by Michael B. Atkins and Maria I. Carlo	
	Predictive Biomarkers for Nivolumab in Metastatic RCC from Checkmate-025	Toni K. Choueiri & Sabina Signoretti
	Predictive Biomarkers for VEGF Inhibitors in RCC	Maxine Sun
	Biomarkers: Where do we go from here?	Brian I. Rini
	Bridging Academia and Industry through Biomarker Work in RCC	Paul B. Robbins
Collaboration in Kidney Cancer Research	Moderated by Toni K. Choueiri and Christopher G. Wood	
	Congressionally Directed Medical Research Programs - Kidney Cancer Research Program	Theresa J. Miller
	Kidney Cancer Research Consortium	Eric Jonasch
	Renal Task Force: Trial Focus on Small Renal Masses and Biomarkers	Michael Jewett
	UT Southwestern Kidney Cancer Program and SPORE	James Brugarolas
	Dana-Farber/Harvard Cancer Center Kidney Cancer SPORE: A Brief Overview	Toni K. Choueiri
	Kidney Cancer Association Research Initiatives	Christopher G. Wood
Translational Variants in Rare Kidney Cancers	Moderated by W. Marston Linehan and W. Kimryn Rathmell	
	Setting the Stage to Research and Collaborations in Rare Kidney Cancer	James J. Hsieh
	Novel Function of the Tumor Suppressor FLCN in Rare Kidney Cancer	Mehdi Mollapour
	Chromophobe RCC	Elizabeth P. Henske
	Novel Mechanism of Pathogenesis for Renal Medullary Carcinoma	Pavlos Msaouel
	Therapeutic Targeting of TFE3 in Translocation Renal Cell Carcinoma	Roberto Pili
	Targeting Papillary Kidney Cancer Variants	Brian Shuch

Figure title and legend

Figure 1. Challenges and controversies facing the RCC research and clinical communities.

Figure 2. Subject areas covered in oral presentations at the Kidney Cancer Research Summit 2019.

<table>
<tr><th colspan="2">Challenges</th></tr>
<tr><th>Addressed at KCRS 2019</th><th>Important unmet needs</th></tr>
<tr><td>• Novel molecular targets for the treatment of renal cell carcinoma.
• Improving drug delivery methods to improve tumor cell specificity, while sparing healthy tissue.
• Novel biological insights obtained through state-of-the-art sequencing methods.
• Finding novel immune checkpoints beyond PD-(L)1 & CTLA-4.
• Improving collaborations at the institutional, national, and international levels between clinicians and translational scientists.
• Improving the characterization of molecular drivers of variant histology.</td><td>• Developing representative cell line models of different renal cell tumor histologies & murine models beyond RENCA to spur on basic and translational science research.
• Leveraging novel methods to target transcriptional factors in RCC (i.e. HIF-2α).
• Better recognizing and tailoring the management of hereditary cancer conditions associated with renal tumors.
• Novel therapeutic options for variant histology RCC subtypes, including tumors with sarcomatoid/rhabdoid features.
• Better defining the clonal evolutional history of renal cell carcinoma tumors and determining how this evolution can lead to therapeutic resistance.</td></tr>
<tr><th colspan="2">Controversies</th></tr>
<tr><td colspan="2">• Biomarkers of response to systemic therapies in renal cell carcinoma:
Are we on the right track or do we need to change course?
• Variant histology renal cell carcinoma:
Are conventional histological definitions too broad?
Could molecularly defined subtypes serve as better means to guide management and therapeutic development for these tumors?</td></tr>
</table>

Figure 2--FINAL