FISCAL YEAR 2017
KIDNEY CANCER RESEARCH PROGRAM
STAKEHOLDERS MEETING

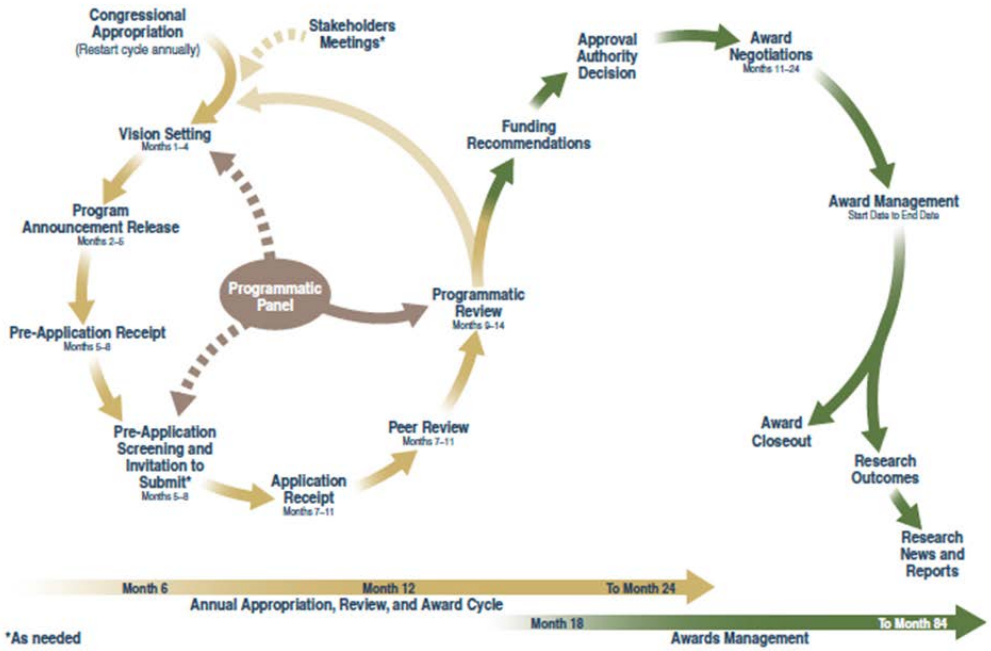
Summary

10/25/2017

Background

The US Army Medical Research and Materiel Command (USAMRMC) is a major subordinate Command of the US Army Medical Command. The Congressionally Directed Medical Research Programs (CDMRP), a subordinate organization within the USAMRMC, is responsible for planning, coordinating, integrating, programming, budgeting, and executing biomedical research funding programs. The CDMRP's flexible execution and management cycle includes the receipt of annual Congressional appropriations and core dollars; inaugural stakeholders meeting for each new program; vision setting meeting; release of full applications; full application receipt; two-tier review; recommendation of grants for funding; and oversight of research grants (Figure 1).

Figure 1. The CDMRP Program Cycle



The basic programmatic cycle for award recommendation is a two-tier system that is dependent on the annual vision setting meeting to guide the upcoming fiscal year investments strategy. During the first year of a program, a stakeholders meeting is held prior to the vision setting meeting. The purpose of the stakeholders meeting includes identifying critical issues facing kidney cancer research and patient treatment, as well as acknowledging the underfunded areas of research and patient care in the field of kidney cancer. Combined with vision setting, the stakeholders meeting reviews the current state of the science and proposes goals for the future of research and patient care to successfully treat kidney cancer. The outcomes of the vision setting meeting set up the program cycle for the fiscal year. Products of the vision setting meeting include the vision and mission statements, the focus areas (if applicable), and the investment strategy, which will be translated into funding opportunities or program announcements.

The CDMRP developed a two-tier model based upon recommendations from a 1993 Institute of Medicine (now called the National Academy of Medicine) report.[1] The recommended two-tier review procedure for research applications was composed of a scientific peer review and a separate programmatic review (Figure 1) to ensure that each program's research portfolio reflects not only the most meritorious science, but also the most programmatically relevant research. The scientific peer review is conducted by an external panel that is recruited specifically for each peer review session and, therefore, is not a standing panel. Peer review involves the expertise of scientists, clinicians, military members, and consumers. The peer review process includes evaluation of applications based on the criteria delineated in the program announcements. Each application is judged on its own scientific and technical merit with respect to the described criteria. The second tier of review, programmatic review, includes discussions by experts in the programmatic field, e.g., kidney cancer for the Kidney Cancer Research Program (KCRP). These experts make up the programmatic panel, a group of scientists, clinicians, lay persons, and members of the military who assess the applications based on the scientific peer review ratings and summaries, portfolio balance, and programmatic intent. Scientifically sound applications that best meet the program's interests and goals are recommended for funding by the programmatic panel. Once approval is received by the decision making authority, awards are made in the form of 1- to 4-year grants.

Kidney cancer research has been funded by the CDMRP for many years under the Peer Reviewed Medical Research Program, Tuberous Sclerosis Complex Research Program, and, most recently, by the Peer Reviewed Cancer Research Program (PRCRP). From FY10 through FY16, the PRCRP invested over $9.8 million (M) in kidney cancer research. In FY17, Congress directed $10M to kidney cancer research in the Department of Defense (DoD) appropriation, thus establishing the Kidney Cancer Research Program. The KCRP's purpose in holding an inaugural stakeholders meeting was to gain an understanding of the current landscape in kidney cancer research and patient care and to build a program that can fill outcomes and knowledge gaps in kidney cancer.

Meeting Objectives

A stakeholders meeting for the FY17 KCRP was held on 23 August 2017. Input from the meeting was used by the programmatic panel to directly shape the overall KCRP goals and priorities.

Purpose

- The stakeholders meeting is a forum for an open dialogue among persons who share a special interest in kidney cancer to identify critical issues facing kidney cancer research and patient treatment, as well as to acknowledge the underfunded areas of research and patient care in the field of kidney cancer.

[1] Institute of Medicine Committee to Advise the Department of Defense on its Fiscal Year 1993 Breast Cancer Program. 1993. *Strategies for Managing the Breast Cancer Program: A Report to the U.S. Army Medical Research and Development Command*. National Academy Press 1-58. Washington, DC.

Stakeholder Participants

- Representatives from non-profit organizations including patient advocates, academia, and government institutions with a special interest in kidney cancer were invited to share broad perspectives on initiatives with the greatest potential to propel the science forward, break down potential barriers in research and patient outcomes, address key knowledge or scientific gaps, and identify potential approaches for the treatment of kidney cancer.

Key Activities

- Roundtable discussions.
- Presentations from the FY17 KCRP programmatic panel members.
- Breakout sessions to identify gaps in specific areas of kidney cancer research and patient care.

Outcomes

- A summary of capability gaps, refinement of the state of the science in kidney cancer, identification of potential challenges, and strategic goals for success.

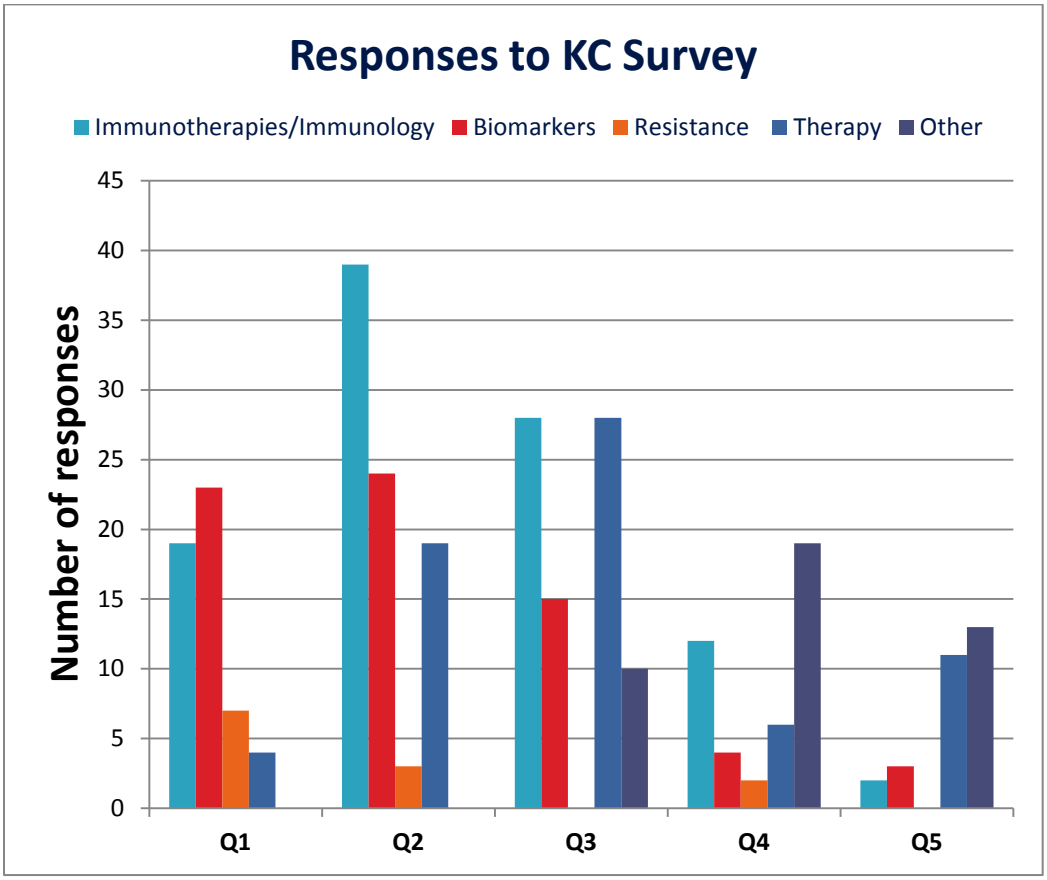
Pre-Meeting Activities

To ensure a broad collection of information from a variety of different stakeholders, the KCRP sent out a survey to 69 potential kidney cancer stakeholders to evaluate both research and consumer needs. The KCRP solicited information to identify (1) knowledge gaps and (2) outcome and product needs along the kidney cancer care spectrum (biology/etiology, prevention, diagnosis/detection, prognosis, treatment, and survivorship issues). The survey questions were:

1. When considering the state of the science in kidney cancer research, identify up to 3 knowledge gaps that, if filled, would have significant impact on patient care.
2. Enter up to 5 strategic goals for *research* in kidney cancer over the next 5 years.
3. Enter up to 5 strategic goals for *patient care* in kidney cancer over the next 5 years.
4. What significant issues in kidney cancer research impede the goal of cure?
5. What research gaps exist in Quality of Life issues after kidney cancer treatment?

The results of the survey were presented at the stakeholders meeting (Figure 2). There was a 30% survey response rate. Responses were tabulated and graphed for presentation and analysis at the stakeholders meeting (Figure 2).

Figure 2. KCRP Survey Responses



The survey results were collated into general categories: immunotherapy/immunology; biomarkers; resistance; therapy; and other responses that included the need for clinical trials, the dearth of young investigators in the kidney cancer field, etc. The survey queried for more than a single response per question and, therefore, multiple responses to the same question could be counted within the same category. For example, the need for immunotherapy treatments in kidney cancer and the gap in understanding the immune response to kidney cancer would both be grouped under immunotherapy/immunology. Immunotherapy/immunology and biomarkers were the most commonly mentioned topics in response to the five survey questions.

Stakeholders Meeting

Taking into consideration space constraints and requirements to keep management costs low, the number of attendees at the stakeholders meeting was capped at 30. Potential participants, who included scientists, clinicians, military clinicians, and patient advocates, were sent invitations to gauge availability and interest. The final stakeholders meeting invitation list aimed to ensure that participants were scientifically and geographically diverse, and broadly represented a variety of key areas important for kidney cancer research. The final roster is presented below.

Participants at the FY17 KCRP Stakeholders Meeting

Mr. Fred Atkin	Action to Cure Kidney Cancer
Dr. Michael Atkins	Lombardi Comprehensive Cancer Center
Dr. Michael Bailey	University of Washington
Ms. Dena Battle	KC Cure
Dr. Carolyn Best	American Urological Association
Mr. Jay Bitkower	Action To Cure Kidney Cancer
Dr. Donald P. Bottaro	Center for Cancer Research, National Cancer Institute
COL Timothy C. Brand	Madigan Army Medical Center
Dr. James Brugarolas	University of Texas Southwestern Medical Center
Dr. Toni K. Choueiri	Dana-Farber Cancer Institute, Harvard University
Dr. Maria Czyzyk-Krzeska	University of Cincinnati
Dr. Emily Dykhuizen	Purdue University
Dr. Stephen Fadem	Baylor College of Medicine
Dr. Robert Figlin	Cedars-Sinai Medical Center
Dr. Ari (Abraham) Hakimi	Memorial Sloan Kettering Cancer Center
Dr. Raquibul Hannan	University of Texas Southwestern Medical Center
Dr. Thai Ho	Mayo Clinic Arizona
Dr. Eric Jonasch	University of Texas MD Anderson Cancer Center
Dr. Payal Kapur	University of Texas Southwestern Medical Center
Dr. Jose Antonio Karam	University of Texas MD Anderson Cancer Center
Mr. Bryan Lewis	VERITAS, LLC
Dr. David McDermott	Beth Israel Deaconess, Harvard University
Dr. Marc Dror Michaelson	Massachusetts General Hospital, Harvard University
Dr. W. Kimryn Rathmell	Vanderbilt University
Dr. Brian Rini	Cleveland Clinic, Taussig Cancer Institute
Dr. Nizar Tannir	University of Texas MD Anderson Cancer Center
Dr. Qing Zhang	University of North Carolina Chapel Hill

Kidney Cancer General Discussion

The stakeholders meeting tackled diverse topics in kidney cancer research and patient care. Using the survey results as a springboard, the stakeholders reviewed the current state of the science in kidney cancer and the state of medical care for patients. During a roundtable discussion, multiple topics were identified as areas for consideration:

- Need for adjuvant therapy to prevent recurrence
- Understanding drug response and resistance in targeted therapies
- Identification of new molecular targets for therapy
- Allocation of funding to rare cancers
- Active surveillance
- Animal models
- Preventing treatment resistance
- Young investigator/clinician career development
- Combination therapies
- Early detection and prevention
- Eliminating the need for systemic therapy through surgery
- Environmental or dietary changes that can affect tumor growth
- Exploring the military relevance in rare kidney cancer subtypes
- Focus on high-impact, high-risk research
- Genetic components of risk
- Disease heterogeneity
- Identification of high risk populations
- Immune response
- Immunotherapies
- Improved quality of life for patients on systemic therapy
- Metabolism
- Minimally invasive measurement modalities
- Patient involvement
- PET imaging
- Predictive biomarkers
- Radiation on primary tumors and metastases
- Recruiting new investigators and engaging with investigators from other fields
- Reducing adverse effects of treatments
- Risk stratification
- Shared resources/knowledge
- Stereotactic radiation therapy
- Tumor microenvironment
- Understanding the unique metabolism of kidney cancer
- Vaccine development

In addition to brainstorming through the roundtable discussion, the stakeholders meeting included presentations by selected members of the FY17 KCRP programmatic panel.

FY17 KCRP Programmatic Panel

Dr. James Brugarolas (Chair)	University of Texas Southwestern Medical Center
Mr. Fred Atkin	Action to Cure Kidney Cancer
Ms. Dena Battle	Kidney Cancer Cure
Dr. Donald P. Bottaro	Center for Cancer Research, National Cancer Institute
COL Timothy C. Brand	Madigan Army Medical Center
Dr. Emily Dykhuizen	Purdue University
Dr. Jose Antonio Karam	University of Texas MD Anderson Cancer Center
Dr. W. Kimryn Rathmell	Vanderbilt University
Dr. Brian Rini	Cleveland Clinic, Taussig Cancer Institute

Summary of Programmatic Panel Member Presentations

Presenter: James Brugarolas, M.D., Ph.D.

Dr. Brugarolas will chair the inaugural year of the KCRP programmatic panel. During the stakeholders meeting he posed a series of questions for the group to consider and discuss. Recognizing that all of the stakeholders gathered may have their own individual research priorities and programs to think about, he nevertheless asked everyone to strive to transcend them to identify the most impactful areas. He encouraged innovation, which is constrained by assumptions about what can or cannot be done. He cited several significant knowledge gaps in kidney cancer research including a lack of predictive biomarkers, a lack of understanding of signaling pathways, and the role of both tumor and microenvironment in treatment resistance and response. He invited the participants to keep an open mind for more considerations as in-depth discussions began.

Presenter: Timothy Brand, COL, M.D.

An active duty physician and urologist, COL Brand explained that kidney cancer is problematic for members of the military as well as the public, and addressing it falls under USAMRMC's mission. He pointed out that methods for risk assessment and stratification would further patient care and treatment.

Presenter: Mr. Fred Atkin

As a kidney cancer patient with a unique perspective to reach out and make a difference within the world of the clinic and the research community, Mr. Atkin listed three knowledge gaps in kidney cancer: understanding of disease heterogeneity, rare kidney cancers, and treatment resistance. Citing his experience with papillary kidney cancer, a less common form of kidney

cancer, Mr. Atkin urged that treatments be developed for non-clear cell kidney cancers. He added that decreasing the toxicity of treatments should also be a program goal, toward improving patients' quality of life.

Presenter: Brian Rini, M.D.
Dr. Rini discussed the need to better understand individual tumor biology in order to develop more effective treatments. He pointed to the limited knowledge of optimal methods of drug delivery and the effectiveness of combined therapies, including mechanisms of response and resistance. Additionally, Dr. Rini addressed the challenge of establishing investigator-initiated trials due to the amount of labor required to initiate such efforts and the difficulty associated with accessing experimental therapeutics.

Presenter: W. Kimryn Rathmell, M.D., Ph.D.
Dr. Rathmell discussed various topics along the spectrum of kidney cancer research and patient needs. She emphasized the importance of understanding metabolic remodeling, the role of chromatin-related mutations, the lack of robust animal models, poor discrimination among kidney cancer subtypes, and the lack of precision medicine strategies for kidney cancer.

To encourage a more focused discussion on specific topics, participants were separated into four different subgroups for the brainstorming session: Immunology, Biomarkers, Resistance, and Targeted Therapy. A summary of each discussion follows:

Summary of Focused Roundtable Discussions

Immunology: Participants in this subgroup identified knowledge gaps within the current state of the science with regard to understanding the role of the tumor microenvironment in evading the body's tumor immune response. The tumor microenvironment's role in regulating kidney cancer progression and metastasis was also recognized. In addition to the tumor microenvironment, participants discussed the development of checkpoint proteins as potential therapeutic targets. The experts disagreed on whether kidney cancer was sufficiently different from other cancer types to necessitate research and trials focused on kidney cancer alone. It was noted that specific genes exhibit a high mutation rate in kidney cancer and that the presence of inflammation may differentiate it from other cancers, thus predicating kidney cancer-centric investigations. Ultimately, the participants agreed that there is a critical need for more advanced clinical trials for kidney cancer patients.

Biomarkers: Results of the survey identified a biomarkers theme, one repeatedly discussed throughout the stakeholders meeting. Effective biomarkers are needed to select patients for active surveillance, to identify high-risk patients for potential screening, to select patients who should receive adjuvant therapy, to select the most effective therapy for patients with metastatic disease, to monitor response to therapy, to identify candidates for cytoreductive surgery, and to improve monitoring for post-surgical chronic kidney disease and follow-up. Different types and categories of biomarkers were discussed.

Resistance: Discussion in this subgroup covered various categories of resistance—innate versus acquired, intrinsic versus extrinsic, and according to treatment type, such as medication or radiation. The group discussed resistance to VEGF/VEGFR targeting agents as well as to

mTORC1 inhibitors. In addition to mechanisms of resistance employed by the tumor, host factors influencing pharmacokinetics (such as drug absorption or metabolism), and the microbiome play a significant role. The participants stated that more effective tools are needed to evaluate resistance at tumor progression. Blood-based measurements that incorporate genomic, epigenomic and metabolomic factors may be of assistance.

Targeted Therapy: Participants noted that single-agent targeted therapies remain the standard of care in kidney cancer given that the majority of patients respond. Nonetheless, these agents involve significant toxicity and responses are seldom durable. Key areas important for the future of targeted therapy in kidney cancer were identified: better selection of patients; the use of combination therapies, such as targeted therapy plus immunotherapy; sequencing strategies to prolong tumor response and overcome resistance; and identification of novel targets, such as DNA repair mechanisms, intracellular signaling pathways, and immunoreceptors.

Summary

In conclusion, the stakeholders sought to find ways to build a better program for kidney cancer research. They recommended providing funding to early career investigators and funding innovative research as key goals for the program. A diverse range of topics was discussed and weighed throughout the day. The open forum of brainstorming welcomed all disparate views on kidney cancer studies. In conclusion, the stakeholders identified the following gaps in research and patient care:

Critical issues in kidney cancer research and patient care topics:

Career Development
- Investment in young investigators
- Investment in established investigators not in KC area
- Bridge gaps in technology in KC

Resource Development
- Biorespositories
- Animal models
- Integration of information and sharing

Risk Stratification
- Indolent, active surveillance
- Heterogeneity
- Resistance

Rare Kidney Cancer Studies

Basic Science Research
- Metabolism
- Epigenetics
- Signaling/proteomics

Micro-Environment
- Immunogenic
- Microbiome effects

Early Detection/Screening

Correlative Studies
- Patient informed markers, responses to treatments not just models
- Precision Medicine needs more information

The stakeholders recognized this inaugural year as KCRP's first step toward combatting kidney cancer and answering the critical issues facing kidney cancer research and patient treatment. The knowledge gaps and needs of the kidney cancer community will form the basis for future strategic goals for the FY17 KCRP.