Kidney Cancer Research Program

Congressionally Directed Medical Research Programs

CDMRP

Department of Defense

U.S. Army Medical Research and Development Command

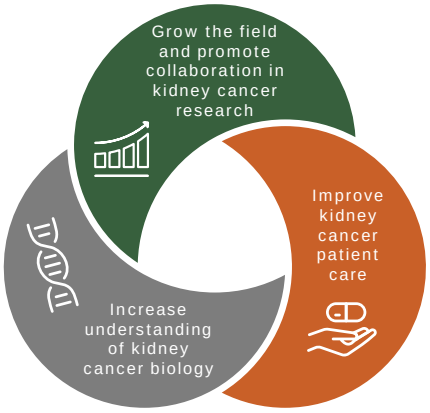
VISION: To eliminate kidney cancer through collaboration and discovery

MISSION: To promote rigorous, innovative, high impact research in kidney cancer for the benefit of Service members, Veterans, and the American public

Kidney Cancer Research Program

History of the Peer Reviewed Kidney Cancer Research Program

Since its inception in fiscal year 2017 (FY17), the KCRP has rapidly become a leader in the drive to eliminate kidney cancer by fostering clinical collaborations and promoting innovative high-impact research. Before FY17, the Peer Reviewed Medical Research Program and Peer Reviewed Cancer Research Program funded and managed kidney cancer research, for a total investment of $13.2 million (M). Thanks to the persistence of kidney cancer advocates, Congress established the KCRP with an initial $10M appropriation to fund kidney cancer research. Continued Congressional support resulted in total KCRP appropriations of $85M from FY17 through FY20 to address much needed areas of investigation. To focus the program's investment priorities the KCRP established three strategic goals, depicted to the right.



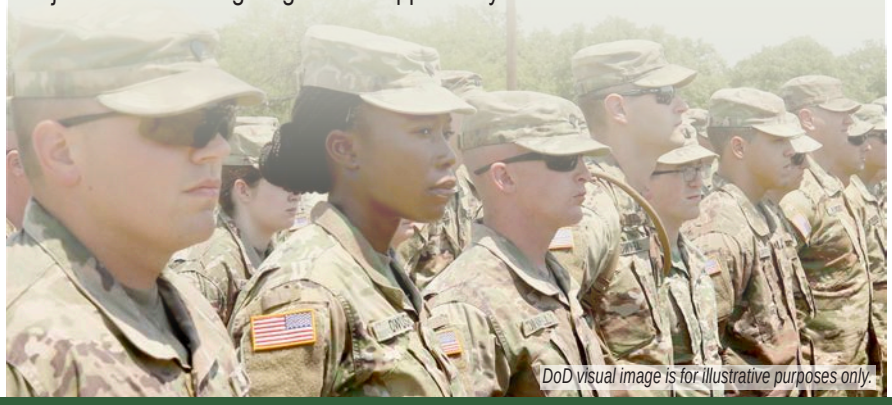
Congressionally Directed Medical Research Programs

History

The Congressionally Directed Medical Research Programs (CDMRP) was established in 1992, when Congress first appropriated funds for the Breast Cancer Research Program. The CDMRP is now a recognized global funding organization encompassing more than 30 research programs, including the Peer Reviewed Kidney Cancer Research Program (KCRP). The strong partnership between the public, Congress, and the military reflects the CDMRP's unique role, particularly because the established two-tier review process involves scientists, clinicians, and consumer advocates at each step. The first tier, peer review, evaluates the scientific merit of each application based on criteria denoted in program announcements. The second tier, programmatic review, compares applications and makes funding recommendations based on scientific merit, program relevance, and portfolio balance.

Programmatic Panel Perspective
COL (Ret.) Timothy Brand

"It has been my distinct honor and pleasure to have served on the KCRP panel. This group of kidney cancer luminaries, consumer advocates, and administrators has worked tirelessly to effectively steward these CDMRP funds with the vision to eliminate kidney cancer through collaboration and discovery. The number and types of awards that have been created has promoted impactful research to the benefit of the active duty Service members, to Veterans, and to the American public. The enormous number and quality of well-written, relevant, and timely award applications has made the selection process for awards a daunting task. I have been tremendously impressed with the diligence, authenticity, effort, and professionalism that each of these panel members has displayed since its formation in 2017. I have no doubt that the stewardship of these Congressional funds has been optimized and that the KCRP will thrive and meet their objectives for as long as given the opportunity."



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Consumer Perspectives

At every step of the program cycle, the KCRP engages consumer advocates—survivors and/or family members and caretakers of persons with kidney cancer actively involved in advocacy, outreach, and support organizations. Importantly, consumers participate in setting the KCRP's vision and priorities and are full voting members of both Peer and Programmatic Review panels. KCRP consumer advocates provide a voice for kidney cancer patients to ensure the program funds groundbreaking, impactful projects that may one day help move the KCRP's vision to eliminate kidney cancer to fruition.

Jay Bitkower: Amateur photographer. Baseball Fan. Nearly 20-year kidney cancer survivor.

"I am honored to have served on the Programmatic Panel for the past 3 years and am very impressed with the quality and breadth of knowledge of the panel members as well as the quality of the research. I am confident that, in time, the KCRP-funded research will have a significant impact on the progress of kidney cancer research and on the lives of those who are stricken by this disease."

Caroline Sample: Two-Time Cancer Survivor Turned Advocate

The thrill of becoming a breast cancer survivor with a cancer-free status was cut short for Caroline Sample a month after returning to work. After falling dreadfully ill, a series of doctor's appointments revealed that there was a large tumor in her left kidney. Pathology results revealed a diagnosis of Clear Cell Renal Carcinoma. When diagnosed, Caroline worked with refugees as a teacher. Her students were always extremely supportive. She underwent nephrectomy surgery and risky treatment with high-dose Interleukin 2. She showed a durable complete response to treatment, meaning that no disease has been detected for over 5 years.

Now retired from teaching, Caroline has worked with KCCure, KCAN, and SmartPatients, leveraging her knowledge from both bouts with cancer to support and educate patients and caregivers. She also works to inform members of Congress about kidney cancer, seeking additional research funding for the National Institutes of Health, National Cancer Institute, and kidney cancer research. Additionally, she serves on the Board of Gateway Community Services Maine, which seeks to support youth, particularly those who are recent immigrants.

Caroline learned of the KCRP process through SmartPatients and KCAN and now represents SmartPatients as a consumer peer reviewer. She has found the scientific community to be "extremely supportive and encouraging to the consumer community." She says, "I wanted to give back since I have been very fortunate in the outcome I've experienced with kidney cancer. When I began the CDMRP process, I felt overwhelmed. The training videos, phone calls, mentor program, and assistance from the SROs (Scientific Review Offers), as well as the support and encouragement of the scientific reviewers, have made it a valuable and rewarding experience. I would encourage others to participate if they are able to do so."

Billy Foster: Journey to Advocacy

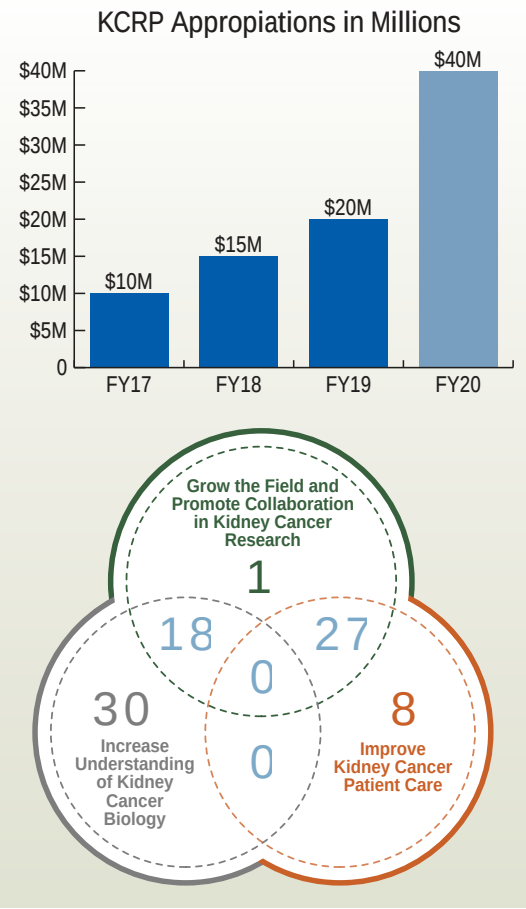
For over 30 years, William "Billy" Foster taught music in Gary, Indiana's public school system and jazz piano at Valparaiso University. He currently produces and hosts the *Billy Foster Jazz Zone* on 88.7 FM WGVE and leads the jazz group, the "Billy Foster Trio." In 1996, he was diagnosed with kidney cancer and underwent a nephrectomy. After the procedure, he was deemed cancer-free. However, in 2007, the kidney cancer returned and metastasized into his lungs, liver, and brain. Fortunately, doctors were able to remove the three brain lesions, but Billy still lives with renal cell tumors in his lungs and liver. From 2008 to 2013, he participated in a clinical trial that kept his tumors stable. After the trial ended, he was prescribed one of the medications that was developed during that time, and to this day his tumors remain stable. Since retiring from the public schools in 2004, Billy continues to perform as a professional jazz pianist and teach at Indiana University Northwest.

From his journey with kidney cancer, Billy was inspired to be involved with advocacy work. He said, "If you outlive the statistics, I believe you have a responsibility to give back." Billy is currently involved in several advocacy organizations, such as the Kidney Cancer Association, the American Association for Cancer Research, the University of Chicago Patient and Family Advisory Council, and This is Living with Cancer-Pfizer. Through these organizations, he has shared his story, hoping to inspire others to get involved. As part of the Kidney Cancer Association, Billy served on an FY18 and FY19 KCRP peer review panel and described his experience as invaluable, giving him insight into the progress being made in kidney cancer research. He is elated to see that funding now exists to address kidney cancer and continuously looks forward to new research developments.

Overview of KCRP Portfolio Investments

Congressional Appropriations

From FY17 to FY20, the KCRP received $85M in Congressional appropriations for kidney cancer research. As of the publication of this book, applications for FY20 were under review.



KCRP Portfolio Investment across the Three Strategic Goals

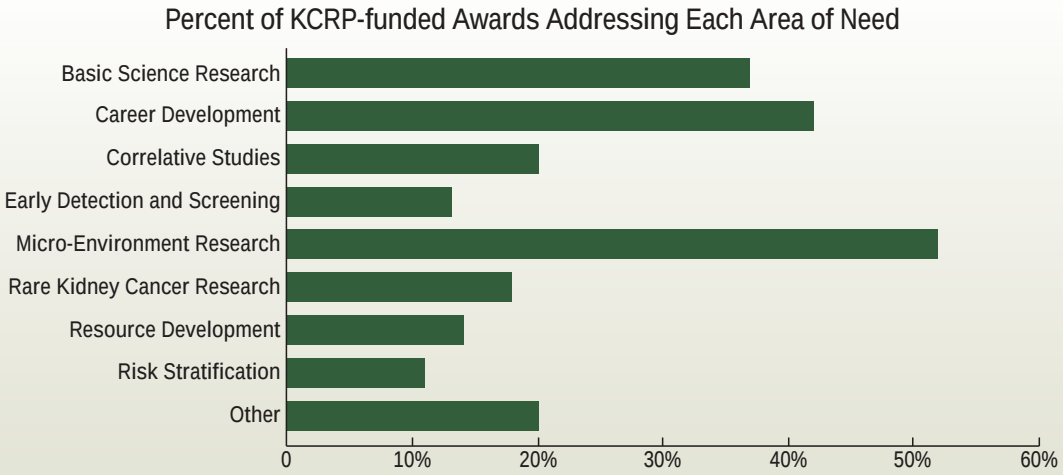
From FY17 through FY19 the KCRP funded 84 awards, each of which aligns to one or more to of the KCRP's three strategic goals:

1) Grow the field and promote collaboration in kidney cancer research. It is the KCRP's ambition to attract, develop, and retain a talented research community, and establish a multi-institutional network of kidney cancer experts to accelerate advances in the field.
2) Improve kidney cancer patient care. Integration of bench research with bedside care is crucial to translating promising kidney cancer research into the clinic. The KCRP aims to support basic research, technology development, and translational research that move innovative concepts to clinical applications.
3) Increase understanding of kidney cancer biology by investing in new ideas and approaches.

The Venn diagram on the right shows the distribution of KCRP-funded awards across the three strategic program goals. Awards either align to a single goal (e.g., 8 awards address the goal to improve patient care), or align to two goals (e.g., 27 awards address both the goal to improve patient care and the goal to grow the field/promote collaboration).

The KCRP Addressing Areas of Need

With input from consumers and kidney cancer experts, the KCRP identified eight Areas of Need in the kidney cancer field: Basic Science Research, Career Development, Correlative Studies, Early Detection and Screening, Micro-environment Research, Rare Kidney Cancers Research, Resource Development, and Risk Stratification. By funding research that addresses these Areas of Need, the program ensures a diversified approach to fulfilling the three strategic goals previously discussed. The chart below displays the KCRP investment across the identified Areas of Need, as well as an additional category—Other—representing funded awards that do not align to any specific Area of Need, but still proposed research supporting the program's strategic goals. Each bar represents the percentage of KCRP-funded awards (FY17–FY19) that align to that particular Area of Need.



(Note: A single project could align to multiple Areas of Need (e.g., a project could be Career Development, Rare Kidney Cancers Research, and Basic Science Research). Therefore, the sum of the percentages does not add up to 100%).

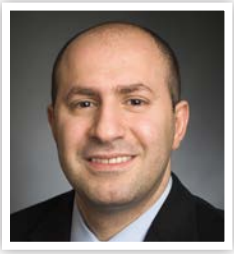
A Novel Mechanism of Pathogenesis for Renal Medullary Carcinoma

Pavlos Msaouel, M.D., Ph.D., The University of Texas MD Anderson Cancer Center

Renal medullary carcinoma (RMC) is the third most common renal cancer among children and young adults; it is predominantly found in young patients of African American descent who have sickle hemoglobinopathies such as sickle cell trait (Sβ) and/or disease (SS). Fewer than 5% of patients with RMC survive more than 36 months, and current treatments provide only a marginal improvement in overall survival. The poor prognosis for those with RMC demands identification of novel targets and mechanisms to support innovative interventions.

Dr. Pavlos Msaouel, supported by a KCRP FY17 Concept Award, studied the association between sickle hemoglobinopathies and development of RMC. The research explored the correlation between sickling of red blood cells (RBC) and predisposition to RMC in mice harboring humanized Sβ and SS. Findings suggested that RBC sickling induced hypoxia and regional microinfarcts, which led to progression of malignancy in renal cells. Additional studies conducted parallel to the mouse studies revealed that extreme dehydration and hypoxia promote RBC sickling, which feed into the pathogenesis loop. This is significant for active duty Service members with sickle hemoglobinopathies who are experiencing dehydration and other stressors. Additionally, the hypertonic microenvironment in the renal medulla facilitates DNA damage while suppressing repair response. This increases the number of chromosomal aberrations in regions containing tumor suppressor genes such as SMARCB1, which is inactive in RMC cases.[1]

Understanding the link between hypoxia, hypertonic conditions, and loss of SMARCB1 tumor suppressor activity is critical to bridging the gap between sickle hemoglobinopathies and development of RMC. Dr. Msaouel expects that further evaluation of the various components of this model will result in RMC prevention strategies, earlier diagnosis, and effective treatment options.



Identifying Predictive Biomarkers for Response to Nivolumab Therapy in Metastatic Renal Cell Carcinoma

Toni Choueiri, M.D.; Sabina Signoretti, M.D., Dana-Farber Cancer Institute

One-third of kidney cancer patients have advanced (metastatic) disease at time of diagnosis.[2] Although patients with metastatic disease typically have a poor prognosis, recent advances in immunotherapy (using the patient's own immune system to attack cancer) have helped more kidney cancer patients achieve favorable outcomes.

Nivolumab is an immunotherapeutic approved to treat advanced kidney cancer. It blocks the function of PD-1, a protein that represses the activity of the immune system, allowing the patient's immune system to target and destroy kidney cancer cells. Twenty percent to twenty-five percent of patients treated with nivolumab demonstrate improved overall survival.[3] Dr. Toni Choueiri and Dr. Sabina Signoretti received an FY17 Translational Research Partnership Award to validate critically needed blood-based and tumor-based biomarkers to predict which patients will respond to nivolumab therapy. Other key members of their team include Drs. Maxine Sun, David Braun, Sachet Shukla, Marios Giannakis, Meredith Regan, Catherine Wu, Eli Van Allen, Gordon Freeman, and others.

Drs. Choueiri and Signoretti gained valuable insight into biomarker candidates using samples collected during Checkmate 025, a phase III clinical trial that compared nivolumab to everolimus in patients with advanced kidney cancer[3]. One study evaluated whether metabolites found in blood, specifically kynurenine (Kyn) and tryptophan (Trp), could be used to predict clinical outcomes.[4] The team found that patients whose Kyn:Trp ratio decreased while being treated with nivolumab had better prognoses than those whose Kyn:Trp ratio increased by more than 50% compared to baseline levels. A second study identified protein polybromo 1 (PBRM1) mutations in patient tumor specimens.[5] Analysis showed that 39.5% of patients who respond to nivolumab had PBRM1 mutations. Additionally, patients with PBRM1 mutations in non-cancerous tissue showed prolonged progression-free survival and overall survival compared to patients with non-mutated PBRM1.

Drs. Choueiri, Signoretti and the team continue to develop these findings. They hope to translate them into clinical practice and increase the number of metastatic kidney cancer patients that benefit from nivolumab therapy.

References:

1. Msaouel P, Tannir NM, and Walker CL. 2018. A model linking sickle cell hemoglobinopathies and SMARCB1 loss in renal medullary carcinoma. *Clinical Cancer Research* 24(9):2044-2049.
2. Sun M, Thuret R, Abdollah F, et al. 2010. Age-adjusted incidence, mortality, and survival rates of stage-specific renal cell carcinoma in North America: A trend analysis. *European Urology* 59(1):135-41 59(1):135-141
3. Motzer RJ, Escudier B, McDermott DF, et al. 2015. Nivolumab versus everolimus in advanced renal-cell carcinoma. *New England Journal of Medicine* 373(19):1803-1813.
4. Li H, Bullock K, Gurjao C, et al. 2019. Metabolomic adaptations and correlates of survival to immune checkpoint blockade. *Nature Communications* 10(1):4346.
5. Braun DA, Ishii Y, Walsh AM, et al. 2019. Clinical validation of PBRM1 alterations as a marker of immune checkpoint inhibitor response in renal cell carcinoma. JAMA Oncology 5(11):1631-1633.

The Kidney Cancer Research Consortium

The KCRP identified the need for multi-site collaborative clinical research initiatives and clinical trials to achieve improved kidney cancer patient outcomes. Acknowledging that there are many hurdles that make the multi-center execution of any clinical trial difficult, in FY17, the KCRP offered a 2-year Consortium Development Award (CDA) to establish a geographically dispersed kidney cancer coalition composed of a coordinating center and at least three clinical trial sites.


Dr. Eric Jonasch


Dr. Hans Hammers


Dr. Moshe Ornstein


Dr. David McDermott


Dr. Naomi Haas


Mr. Dewey Stringer (Consumer)


Ms. Brenda Knapp (Consumer)

Dr. Jonasch of MD Anderson Cancer Center received the FY17 CDA, forming the Kidney Cancer Research Consortium (KCRC) to execute informative, translationally focused, multi-center clinical trials. The original KCRC consisted of MD Anderson Cancer Center as the coordinating center and three clinical trial sites—the University of Texas Southwestern Cancer Center, led by Dr. Hans Hammers; The Cleveland Clinic Foundation Taussig Cancer Center, led by Dr. Moshe Ornstein; and the Beth Israel Deaconess Medical Center, led by Dr. David McDermott. A Steering Committee was formed from the principal investigators of each site and a kidney cancer consumer, Mr. Dewey Stringer, to lead the development of the KCRC. The founding members of the KCRC came together to address challenging issues in the regulatory approval and contracting processes, as well as standardization for data and tissue collection. As such, the efforts of the KCRC over the ensuing 2 years of the CDA revolved around five major goals:

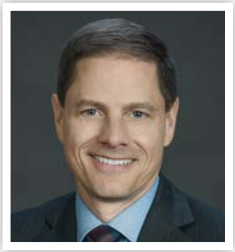
1. *Creating an effective governance and management structure*
2. *Developing a harmonized protocol approval and monitoring process*
3. *Applying a flexible and efficient data management platform*
4. *Creating an innovative therapy testing and sample analysis infrastructure*
5. *Creating industry and philanthropic partnerships*

For FY19, the KCRP offered a Clinical Consortium Award to continue supporting the infrastructure needs of a network of exceptional institutions and investigators with the goal of rapidly executing kidney cancer trials. Dr. Jonasch and MD Anderson Cancer Center were selected to remain the coordinating center of the KCRC, and the three clinical trial sites selected were—the University of Texas Southwestern Cancer Center, still led by Dr. Hammers; the Beth Israel Deaconess Medical Center, still led by Dr. McDermott; and a new member, Abramson Cancer Center at Penn Medicine, led by Dr. Naomi Haas. Mr. Stringer remains on the Steering Committee as a kidney cancer consumer, and Ms. Brenda Knapp has joined the Steering Committee as a second consumer.

As of fall 2020, the KCRC has accomplished the first three of the five major goals and is well-poised to permit more rapid initiation of and accrual to clinical trials that would otherwise be difficult to complete at any single center. The KCRC will open trials for patients with all types of renal cell carcinoma, including rarer forms like medullary, papillary, and chromophobe renal cell carcinomas. Ultimately, the long-term impact of the KCRC on patients with kidney cancer will be the discovery of more specific treatment approaches, driven by a convergence of an improved understanding of renal cell carcinoma biology and therapies that are targeted to the right patient subpopulations.

Academy of Kidney Cancer Investigators

Developing a network of early-career researchers who are committed to careers as kidney cancer researchers is also critical to accelerating advances in kidney cancer treatment. To address this need, in FY19, the KCRP offered inaugural Academy of Kidney Cancer Investigators (AKCI) funding opportunities. The AKCI brings together an Academy Dean with a cadre of ECIs in a unique, interactive virtual academy providing intensive mentoring, national networking, collaborations, and a peer group for junior faculty emerging as future leaders of kidney cancer investigation.



Dr. Brian Rini, an Ingram Professor of Medicine and Chief of Clinical Trials at Vanderbilt Ingram Cancer Center, was awarded the inaugural FY19 Academy of Kidney Cancer Investigators – Dean Leadership Award. He brings to the Academy over 20 years of experience in clinical and translational kidney cancer research and extensive experience mentoring kidney cancer ECIs. He invested time and effort that is critical to the success of the AKCI to understand the needs of kidney cancer ECIs, identify common barriers to achieving success, and brainstorm about how to overcome those barriers. As such, Dr. Rini identified five essential components for a successful and impactful AKCI:

1. *Commitment. The AKCI will foster the commitment of ECI/mentor pairs to pursue impactful careers in kidney cancer.*
2. *SMART Goals. ECIs will develop specific, measurable, achievable, relevant, and time-bound (SMART) goals to ensure they stay focused and can identify hurdles when they arise.*
3. *Networking. The AKCI will provide ECIs with visibility and networking opportunities to establish their standing in the kidney cancer field.*
4. *Feedback. ECIs will receive structured guidance and feedback to facilitate the achievement of their SMART goals.*
5. *Collaboration. ECIs will experience enhanced collaboration and interaction among a diverse population of kidney cancer researchers.*

To ensure the most robust experience for the AKCI ECIs, Dr. Rini formed an Advisory Board of kidney cancer researchers and clinicians with diverse skill sets that span laboratory science, translational medicine, urologic expertise, and clinical trials experience. The geographic, gender, seniority, and expertise diversity of this panel will provide the ECI/mentor pairs with a full spectrum of resources, visibility, and opportunities for career advancement.

Members of the Advisory Board:

James Brugarolas, M.D., Ph.D. (Advisory Board Chair) – University of Texas Southwestern

Laurence Albieges, M.D., Ph.D. – Gustave Roussy Institute (France)

Sumanta Kumar Pal, M.D. – City of Hope Comprehensive Cancer Center

David F. McDermott, M.D. – Beth Israel Deaconess Medical Center

Marie (Celeste) Simon, Ph.D. – University of Pennsylvania

Robert G. Uzzo, M.D. – Fox Chase Cancer Center

The three ECIs selected to receive FY19 Academy of Kidney Cancer Investigators – Early-Career Investigator Awards:

"Understanding CD8+ T-Cell **Specificity and Function in Renal** Cell Carcinoma"

David Braun, M.D., Ph.D. (Primary Mentors: Toni Choueiri, M.D., and Catherine Wu, M.D.), Dana-Farber Cancer Institute

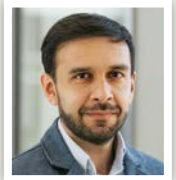
Proposal Abstract: https://cdmrp.army.mil/search.aspx?LOG_NO=KC190128

"Exploiting Epigenetic Dysregulation to Identify Targetable Vulnerabilities in ccRCC"

Abhishek Chakraborty, Ph.D. (Primary Mentor, David F. McDermott, M.D.), Cleveland Clinic Foundation

Proposal Abstract: https://cdmrp.army.mil/search.aspx?LOG_NO=KC190207

"Epigenetic Modifications of Cytosines in Clear Cell Kidney Carcinogenesis and Survival"



Lucas Salas, M.D., Ph.D. (Primary Mentor: James Brugarolas, M.D., Ph.D.), Dartmouth

Proposal Abstract: https://cdmrp.army.mil/search.aspx?LOG_NO=KC190133

Researchers, clinicians, and patient advocates who attended the 2019 Kidney Cancer Research Summit, held in Philadelphia, PA.

Choueiri TK, Atkins MB, Bakouny Z, et al. Summary from the First Kidney Cancer Research Summit, September 12-13, 2019: A Focus on Translational Research. *J Natl Cancer Inst.* 2020 May 2:djaa064. doi: 10.1093/jnci/djaa064. Epub ahead of print. PMID: 32359162.

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