Exhibit 378

EXPERT REPORT ON THE REVIEW OF GENETIC TESTING RECORDS FOR JACQUELINE TUKES – RENAL CELL CARCINOMA
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PURPOSE

The purpose of this report is to provide an opinion regarding the results of genetic testing and causation of renal cell carcinoma (RCC) in Jacqueline Tukes based on a review of the medical records. It will also provide a general overview of cancer biology and the biology of RCC. The opinions expressed in this report were formulated following a comprehensive literature review of the publicly available scientific evidence related to RCC and the genetic markers utilized to screen for the disease in the patient. Whenever possible, peer-reviewed scientific data will be used to support the opinions expressed in this report.

BACKGROUND AND QUALIFICATIONS

I received my Bachelor of Science (B.S.) degree in Biology from East Carolina University in 1997, with a concentration in Molecular Biology and Biotechnology. Following the completion of my B.S., I began work as a Laboratory Technologist at Laboratory Corporation of America (Lab Corp) in the Paternity Testing Division in 1997 and worked in this position until 2001. While at Lab Corp, my job was to conduct DNA based testing of human specimens using the same and similar techniques to those used in the current case. This included all aspects of DNA testing from specimen handling, to extraction, sequence variation analysis, data assessment and interpretation, validation, and quality control/quality assurance. While working second shift and weekend shifts full time at Lab Corp, I began concurrent graduate training at the University of North Carolina at Greensboro. I received my Master of Science (M.S.) degree in Biology in December 2000. My M.S. thesis focused on the development of molecular assays to detect toxic microorganisms in the environment. Following my graduation, I was employed as a Research Analyst at Duke University and the Duke University Medical Center at the Center for Human Genetics. In this position, I conducted research identifying human genetic mutations associated with a variety of diseases. I routinely utilized sanger sequencing and denaturing high-performance liquid chromatography (DHPLC) to identify variations in DNA from human patients. This work was an effort to identify gene mutations for use in research, diagnostics, and therapeutic development. Concurrently, I also worked part-time as a Molecular Biology Laboratory Technologist at North Carolina State University, assisting members of the Center for Applied Aquatic Ecology in utilizing

the molecular biology assays that I developed as part of my M.S. research in screening environmental samples for toxic microorganisms. My M.S. research was awarded the University of North Carolina at Greensboro University Excellence Award. Together, my education and work experience provided me with extensive applied research expertise in the fields of molecular biology, biotechnology, environmental science, and human genetics.

I entered the Doctor of Philosophy (Ph.D.) graduate program at the University of North Carolina at Chapel Hill (UNC) in 2002 and completed my Ph.D. in Genetics and Molecular Biology in 2006. My Ph.D. Dissertation focused on defining the roles of G Protein-Coupled Receptors in the Neuropathophysiology of Asthma. Asthma is a complex genetic disorder with environmental influences and my research sought to better define the interplay between genetics, the immune system, and environmental factors in driving disease processes. This work defined mechanisms associated with a group of receptors that could be therapeutically targeted in human patients to alleviate asthma exacerbations. My research involved extensive use and development of mouse models of human diseases. Together, my Ph.D. graduate training provided me with extensive expertise developing and utilizing mouse models of human diseases and pre-clinical rodent studies. As part of my Ph.D. education and training, I gained further applied expertise in genetics, molecular biology, immunology, environmental exposure science, animal models, human clinical studies, and drug studies in rodents.

Upon completion of my Ph.D. in December 2006, I immediately began my Postdoctoral Training in Immunology and Cancer Biology at UNC in 2007 at the Lineberger Comprehensive Cancer Center and the UNC School of Medicine. My postdoctoral training focused on defining mechanisms associated with how the immune system recognizes and responds to microbes, chemical agents, and cellular damage that contributes to cancer pathogenesis. My work in this field contributed to a significant paradigm shift in how cancer biologists view the relationship between immune system signaling, inflammation, and tumor development. Specifically, my work has contributed to the understanding that the innate immune system functions to maintain balance (or homeostasis) in tissues exposed to insults and injury. My work has revealed that chronic inflammation can function as a tumor promoter – which is/was already well established; however, immune suppression can also function as a tumor promoter, depending on the type of cancer, the mechanism of immune system modulation, and the tumor microenvironment. I have dubbed this the “Goldilocks Conundrum,” where increased inflammation (too hot) or immune suppression (too cold) can each drive cancer depending on the tumor microenvironment. This work has revealed that any insult that shifts the immune system balance, either towards inflammation or suppression, has the potential to enhance disease pathogenesis, including cancer. Cancer is a highly complex

disease whereby reduced immune system recognition can serve as a hallmark of cancer and tumor promoting inflammation is considered an enabling characteristic. My research in this field has been published in multiple high impact journals and has been highly cited by the scientific community. During my postdoctoral training, this research and my graduate research was awarded the UNC Chapel Hill Graduate Education Advancement Board's Impact Award for research that contributes to the health and well-being of communities and citizens of North Carolina and beyond. I was also awarded the UNC Chapel Hill Postdoctoral Award for Research Excellence, which recognizes the research potential in selected postdoctoral trainees at UNC. Finally, my postdoctoral research was also awarded the Lineberger Comprehensive Cancer Center Joseph S. Pagano Award, which recognizes top research published in high impact journals for the year awarded (2010).

In 2012, I was hired as a tenure-track Assistant Professor of Inflammatory Diseases at Virginia Polytechnic Institute and State University (Virginia Tech), where I continue to serve as a faculty member in the Department of Biomedical Sciences and Pathobiology. I was awarded tenure and promoted to Associate Professor in 2019 and Full Professor in the Spring of 2023. In addition to my tenured faculty position, I also currently serve as the Assistant Department Head for Research Support and I am also appointed as a Professor in the Department of Basic Science Education at the Virginia Tech Carilion School of Medicine. My independent research programs continue to be focused on understanding the role of the immune system in host-pathogen interactions, inflammatory diseases, and cancer. The ***cancer pillar*** is the most relevant to the current report. My research team has become internationally recognized for our expertise in evaluating the tumor microenvironment, innate immune system signaling, systemic anti-tumor immune responses, and therapeutic assessments in cancer. Indeed, my cancer research has resulted in several high impact publications, including multiple first author or corresponding author manuscripts in *Immunity*, *The Journal of Experimental Medicine*, and *The Journal of Immunology*[1-4]. Complementing the cancer pillar, I also routinely incorporate the development of animal models for use in human preclinical studies and studies in human patients into my research program. My team has become internationally recognized for our animal model capabilities and routinely collaborate with diverse multinational research teams from academia, government, and industry. Our animal modeling work has resulted in multiple transdisciplinary publications in the journals *Science*, *Immunity*, *Angewandte Chemie*, *Advanced Science*, and *EBioMedicine*[5-10].

In the area of cancer immunology, as I alluded to above, there is an intimate link between dysregulated inflammation and cancer. My laboratory is utilizing both common and novel models of cancer and cutting-edge analysis tools to dissect the interplay between elements of the tumor

microenvironment, local immune system recognition, and systemic immune responses to find cures. Our research focuses on mechanisms associated with both innate and adaptive immune system signaling. For example, I was one of the first people to identify a role for a family of immune system receptors in maintaining the balance of inflammation and modulating the development of tumors in the gastrointestinal system. This unique finding resulted in publications in the journals *Immunity and The Journal of Experimental Medicine*[1, 2], with subsequent follow up publications in a variety of high impact journals over the last decade[4, 11-15]. I am now extending these findings to other regulators of the immune system and exploring the contribution of this family of receptors in multiple types of cancer with a connection to aberrant immune system function, including immune system cancers, pancreatic cancer, and breast cancer. This also includes recent studies focused on better defining systemic adaptive immune system activation, B cell proliferation and responses, improving T cell activation and function, and the exploration of novel therapeutic strategies to enhance anti-tumor immunity.

Of relevance to the current report, a significant amount of my research focus is centered on dissecting exogenous drivers of cancer and therapeutic targets. Exogenous agents and insults can significantly alter both the local tumor microenvironment and systemic anti-tumor immune responses. Once tumors form, drugs and therapeutic approaches can also alter these responses to return the system to balance (or homeostasis). Understanding these processes are critical for both effective animal modeling of the tumor of interest and in evaluating therapeutics. I routinely utilize chemicals to induce tumors in mice, rats, and pigs. I typically follow up these studies evaluating drugs and/or therapeutic approaches to cure the induced tumors. Indeed, the translation of basic research findings from “bench-to kennel-to bedside” is major goal of my research team. My group has participated in several highly interdisciplinary collaborations with clinicians, engineers, and basic scientists to assist them in translating their novel ideas and concepts into viable treatment strategies targeting a diverse range of infectious diseases, immune system disorders, and cancer. We have developed a wide range of novel *in vitro*, *ex vivo*, and *in vivo* models, which have played essential roles in evaluating therapeutic technologies, drugs, and treatment approaches. These interdisciplinary collaborations are often highly challenging, but also highly rewarding for both me and my research team. Our work has been published in a variety of journals including *Frontiers in Immunology, EBioMedicine, Angewandte Chemie*, and *Advanced Science*[5-10].

To date, I have published over 120 research papers in leading peer-reviewed journals. I have also published 3 books associated with the development of mouse modes to study human diseases, and contributed 12 book chapters related to this topic. I have been awarded 1 patent

and disclosed 3 others related to novel therapeutic strategies that can alter the tumor microenvironment and improve cancer treatment. My publications have been cited over 11,122 times and my h-index is 50. The h-index is a quantitative measure that captures research output and is designed to provide a snapshot of an individual's research performance. It is useful for comparing researchers in similar fields and similar career lengths. In this case, my h-index of 50 is considered outstanding for my field and time as an independent scientist. Complementing my publication record, I have presented over 186 invited talks, seminars, lectures, keynotes, and presentations at scientific research conferences and served as an invited chair or moderator of 10 sessions or workshops. Together, my research programs and those that I collaborate with have brought in over $20 million in research grant funding.

Since starting my own laboratory at Virginia Tech, I have become an internationally recognized leader in the fields of immunology and cancer biology. My research has been nationally and internationally recognized, for example in 2014 I was awarded the Chambers-eBioscience Memorial Award from the American Association of Immunologist for my work as an early-career scientist in cancer biology. I am a current or past member of several professional societies in my fields, including the American Association of Immunologists, the Society for Mucosal Immunology, the American Association for the Advancement of Science, the Society for Leukocyte Biology, the American Society for Microbiology, and the American Association for Cancer Research. As a highly active member in most of these organizations, I have held multiple leadership positions, including service on the Board of Councilors, and serving as Chair for multiple committees and professional events.

In addition to my professional service, I also serve on multiple local, regional, national, and international Grant Review Committees and Study Sections where I directly contribute to research funding decisions. I have served on grant review committees and study sections advising the United States government, as well as, international governments, including the European Research Council, the United Kingdom, Israel, Austria, and Switzerland. To date, I have served and continue to serve on 33 study sections as either a standing or *ad hoc* member. This is in addition to my service on grant review panels for various international Foundations, such as Cures Within Reach, The Wellcome Trust, and the Crohn's and Colitis Foundation. Beyond grant review panels, I am also routinely invited to review research submitted for publication in leading scientific journals. For example, over the last 3 years, I have reviewed manuscripts for *Science*, *Proceedings of the National Academy of Sciences*, *The Journal of Clinical Investigation*, *Cell*, *Science Advances*, *iScience, Cancer Research,* and others. In sum, I have reviewed 64 manuscripts in the last 3 years. In addition to my peer-review service, I am also a Deputy Editor

of the *Journal of Leukocyte Biology* and just completed two terms as an Associate Editor for the *Journal of Immunology*, which are both senior editor positions with these leading journals.

Complementing my research education and training, I also completed a Master of Business Administration (M.B.A.) degree with a concentration in Bioscience Management in 2012 from North Carolina State University. I attended Business School while completing my postdoctoral training. The focus on Bioscience Management is a natural pairing with my research background. My M.B.A. provided me with extensive didactic instruction in the operations and practices of science and technology focused businesses. This includes formal training in innovation management, marketing management, supply chain management, technology entrepreneurship and commercialization, entrepreneurship, and financial management. I currently serve or have served on the Advisory Boards of 3 different businesses in the biomedical research space. Leveraging this training and education, I started a small consulting business in 2019 where I am currently the owner and president of Allen Consulting and Management, LLC. We specialize in helping clients in the bioscience sector solve their unique business needs. As part of our business, we also routinely assist clients in better understanding the often confusing and seemingly conflicting nature of the scientific literature and provide insight into complex biological processes, such as the biology of cancer.

RELIANCE LIST

To prepare for this report, I have reviewed the following materials:

1) the medical records for Jacqueline Tukes from UNC Healthcare, provided to me by attorneys for the plaintiff;
2) the current scientific literature relating to cancer biology and the biology of RCC from peer reviewed sources available through the National Library of Medicine and accessible through PubMed;
3) background information on RCC provided by reputable on-line sources (i.e. the National Cancer Institute);
4) background information associated with the genetic testing, derived from the manufacturer, vendors, medical centers, and clinical testing companies, including the company that conducted the analysis (i.e. Invitae).

A complete list of my reliance materials is included as a References section.

THE BIOLOGY OF CANCER

The United States declared war on cancer in 1971[16] and over the last 50 years the research and medical communities have made rapid advances in our understanding of cancer biology. The foundation of this progress has been the initial discoveries and characterization of mutations in our genes that result in cells either gaining functions that promote tumor development or losing the ability to suppress tumor formation[16, 17]. In the 1970s and 1980s, most of the research on cancer focused on understanding these different genetic mutations and their functional consequences. Since the initial focus on gene mutations, the field of cancer biology has significantly expanded to better encompass the complexity and highly personalized nature of cancer. It is now clear that tumors are significantly more complex than masses of proliferating cancer cells and the accumulation of genetic mutations[17]. Indeed, there is consensus in the field that genetic mutations certainly enable and contribute to tumor development; however, genetic mutations alone are rarely sufficient to result in cancer. We now recognize that cancer is a complex, multi-step, and multifactorial disease.

Until about 20 years ago, the field of cancer research was mostly driven by a **reductionist focus** on the cancer cells themselves and the mutations that drive tumorigenesis (**Figure 1**). While this view produced a foundational body of knowledge, it is now widely recognized that to understand tumor biology and the underlying causes of cancer, the field has moved beyond this reductionist view and now applies a **heterotypic cell biology approach** (**Figure 1**)[17]. It is now clear that tumors are more than just a collection of cells with select mutations. In the cancer cells themselves, cancer occurs through the culmination of a series of defects in biological signaling pathways and functions. For example, it is often useful to think about cancer signaling pathways within the cancer cell as a circuit model, similar to an electronic circuit, where each pathway is interconnected and has multiple regulators to ensure proper function and prevent tumor formation (**Figure 2**)[17]. The schematic shown in **Figure 2** represents many of the key, **cell intrinsic**, signaling pathways that can be altered during tumor development. As observed in **Figure 2**, changes in gene expression play a central role in the transformation of a cancer cell[17]. However, defects in any of these signaling pathways, alone or in combination, can ultimately result in uncontrolled cell proliferation and tumor formation[17]. Many of these signaling pathways can, and are, altered through **external stimuli**, such as exposure to chemicals. Not all external stimuli need to induce mutations to promote cancer. Many can induce tumorigenesis through inhibiting or activating signaling pathways, such as those shown in **Figure 2**[17].

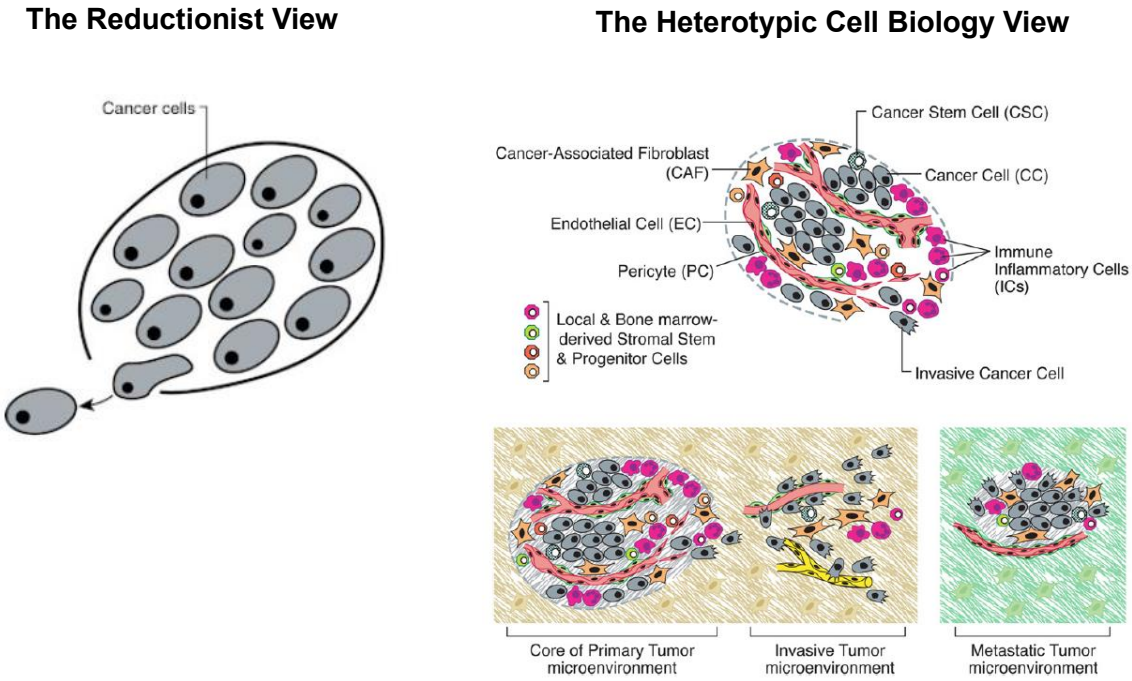


Figure 1. The Reductionist View versus the Heterotypic Cell Biology View (reproduced from Reference 17)

In addition to these cell intrinsic mechanisms, there are also cancer cell **extrinsic factors** that can impact tumor development. Applied research typically focuses on the tumor microenvironment, which includes not only the cancer cell, but also all of the healthy cells surrounding the tumor that directly impact tumor progression, escape from containment, and metastasis (**Figure 1**)[17]. Extrinsic factors that impact the healthy cells in the tumor microenvironment, such as altering the immune system that is responsible for targeting and killing cancer cells or changing the density of the structural cells that are surrounding and containing the developing tumor, can directly result in significantly increased disease progression[17].

Finally, outside of the tumor microenvironment, it is now clear that we must also consider the individual. Cancer is a highly individualized disease, with significant heterogeneity between patient populations. This is clinically observed by the high level of disease variation between patients with the same types and sub-types of cancers. The drivers of this heterogeneity are largely undefined, thus any assumptions used in population scale modeling and epidemiology studies are minimal. These **patient intrinsic factors** include commonly evaluated quantifiable factors, such as lifestyle and occupational and/or environmental exposure to chemicals. However, at a biological level, there is significantly more complexity that is often not accurately assessed or

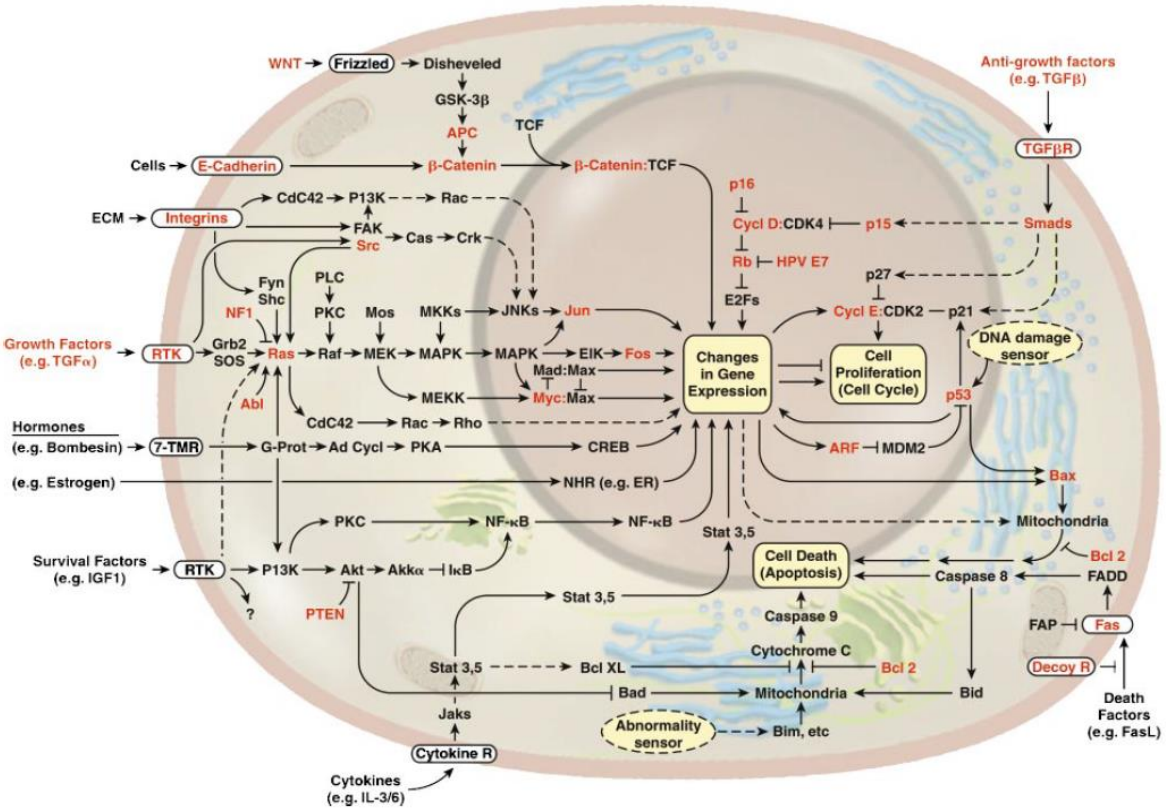


Figure 2. An Integrated Circuit Model of the Cell (reproduced from Reference 17). It is often useful to view the signaling networks that are associated with cancer as a circuitry model, like an electronic integrated circuit. In this schematic, the complexity and the interrelationship of each pathway are more easily observed. The dysfunction of one signaling pathway or mechanism impacts the whole system, increasing the likelihood of cancer. At the genetic level, some of the genes known to be functionally altered are highlighted in red. Alterations can be driven by mutation or through defects in gene regulation at any of 5 different levels within the cell, including epigenetic, transcriptional, post-transcriptional, translational, or post-translational levels.

accounted for in attempting to establish cancer causation. For example, immune system function can significantly vary between individuals. In the context of cancer, a normally functioning immune system is critical to find and kill cancer cells and to contain tumors once they have formed. However, if the immune system is hyperactive during the early stages of tumor development, the mediators produced during inflammation can promote tumor development[18]. Conversely, any intrinsic or extrinsic stimuli that suppresses immune system function, such as environmental exposure to a chemical, can result in the loss of tumor containment and result in rapid disease progression[18]. In addition to the balance that must be maintained in the function of the immune system, other patient intrinsic factors have also been realized. As another example, it is now clear that the composition of the microbes that live in and on our bodies (the so-called microbiome) can

also significantly impact our overall health and disease progression. These microbes form a synergistic relationship with our bodies and can directly regulate metabolism, nutrient intake, immune system function, chemical breakdown, and many other biological functions. The composition of the microbiome varies significantly between individuals, impacting these critical functions. Indeed, the microbiome has been directly linked to a variety of diseases, including cancer[19]. Thus, any extrinsic agent, such as a chemical, that alters the composition of the microbiome has the potential to significantly contribute to cancer[19].

As evident from the discussion above, cancer is a complex, multi-step, and multifactorial disease that can be difficult to conceptualize. In 2000, 2011, and 2022 Douglas Hanahan (UCSF) and Robert Weinberg (MIT) published a series of review articles focused on what we now refer to as "The Hallmarks of Cancer"[17-19]. The original "The Hallmarks of Cancer"[17] and the follow up "Hallmarks of Cancer: The Next Generation"[18] are each one of the most highly cited (with well over a combined 100,000 citations) and influential scientific articles of all time. In this series of works, culminating in the most recent publication in the Journal *Cancer Discovery* in 2022[19], Hanahan and Weinberg frame cancer as a manifestation of 10 essential alterations in cell physiology and biological function that collectively drive malignant growth **(Figure 3)**. These 10 alterations are defined as Hallmarks that the authors indicate are shared by most human tumors[17-19]. Every decade, the work has been revisited, with new hallmarks being added as the field of cancer biology has progressed. Currently, the 10 hallmarks are identified as follows: 1) Sustaining Proliferative Signaling; 2) Evading Growth Suppressors; 3) Avoiding Immune Destruction; 4) Enabling Replicative Immortality; 5) Activating Invasion and Metastasis; 6) Inducing or Accessing Vasculature; 7) Resisting Cell Death; 8) Reprogramming Cellular Metabolism; 9) Unlocking phenotypic Plasticity; and 10) Senescent Cells **(Figure 3)**. In addition to these 10 Hallmarks, the authors also identify 4 "Enabling Characteristics", which are basically defined as insufficient to result in cancer alone; however, their acquisition contributes to the development of cancer and can enhance some of the hallmarks[18, 19]. The 4 enabling characteristics are identified as follows: 1) Tumor Promoting Inflammation; 2) Genome Instability and Mutation; 3) Non-mutational Epigenetic Reprogramming; and 4) Polymorphic Microbiomes (**Figure 3**). Together, each of these changes in cellular functions and processes, represents the acquisition of new capabilities that allows the cell to circumvent our body's anti-cancer defense mechanisms[17-19]. It is generally agreed in the field of cancer biology that **together the Hallmarks of Cancer provide a conceptual framework for understanding cancer biology and are a useful tool for distilling the complexity of cancer phenotypes and genotypes into a set of underlying principles[17-19].**

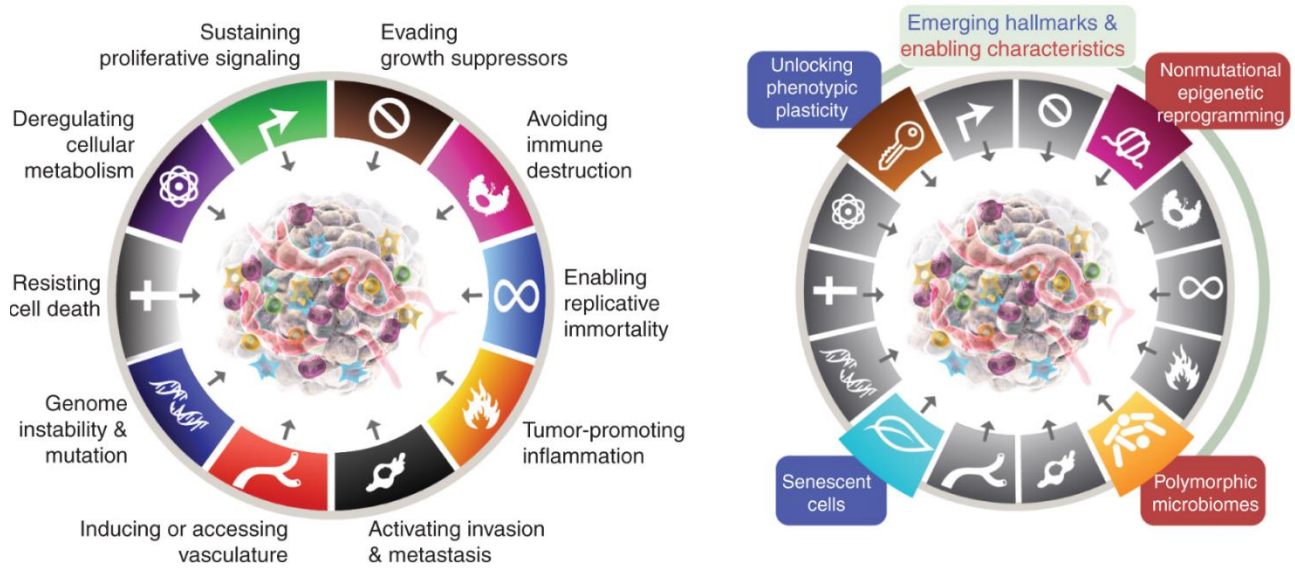


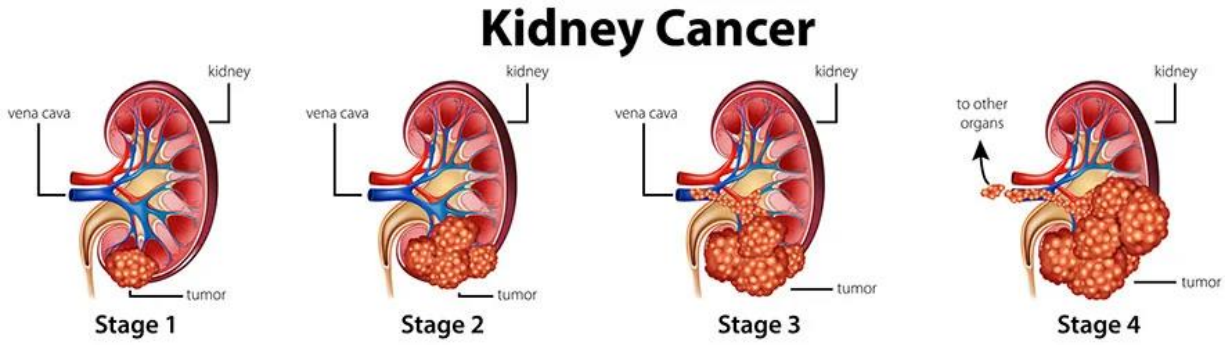
Figure 3. The Hallmarks of Cancer, circa 2022 (reproduced directly from Reference 19). Prior to 2022, the Hallmarks of Cancer embodied 8 hallmarks and 2 enabling characteristics. These are shown in the schematic above in the Left panel. The 8 hallmarks include Sustaining Proliferative Signaling; Evading Growth Suppressors; Avoiding Immune Destruction; Enabling Replicative Immortality; Activating Invasion and Metastasis; Inducing or Accessing Vasculature; Resisting Cell Death; and Reprogramming Cellular Metabolism. The 2 enabling characteristics include Tumor Promoting Inflammation and Genome Instability and Mutation. In the most recent update by Hanahan in 2022[19], the following 2 additional "emerging hallmarks" are introduced as Unlocking Phenotypic Plasticity and Senescent Cells. The 2 additional enabling characteristics are introduced as Non-mutational Epigenetic Reprogramming and Polymorphic Microbiomes.

RENAL CELL CARCINOMA

Renal cell carcinoma (RCC) is a cancer that forms in the kidney (**Figure 4**). The cancer occurs in cells that form the lining of the tubules, which are the small tubes in the kidneys that filter and clean the blood and remove waste products to make urine[20]. RCC occurs when renal cells undergo biological changes (i.e. acquire Hallmarks of Cancer; **Figure 3**) that enhance their ability to grow and divide into new cells. According to the National Cancer Institute, there are multiple risk factors associated with RCC, but many do not directly cause cancer[20]. Rather, these risk factors typically increase the chance of DNA damage (i.e. increase genome instability and mutation) in cells that result in renal cell carcinoma[20]. Risk factors can be anything that increases the chance that a person gets a disease. For RCC, the most common risk factors include smoking, excess body weight, and high blood pressure. Certain genetic diseases can also increase the risk of RCC, including von Hippel-Lindau disease or hereditary papillary renal cancer[20]. Having one or more of these risk factors does not mean that a person will get RCC. Indeed, many people with

these risk factors will never develop cancer, while others with no known risk factors will[20]. Common tests used to diagnose RCC include ultrasound exam, blood chemistry, urinalysis, CT scan, MRI, and biopsy[20]. After diagnosis, additional tests are commonly conducted to stage the disease[21] (i.e. determine if metastasis, also known as cancer spread, has occurred and to determine the extent of cancer in the body), which can include additional CT and MRI scans, chest X-ray, and bone scan[20]. Additional testing is also common to assist with determining genetic risk factors and to assist with disease management. Treatment options for RCC typically include surgery, radiation therapy, immunotherapy, and targeted therapies[20]. In the United States, the American Cancer Society estimates that 29,230 new cases of kidney cancer will be diagnosed in women in 2024 and 4,940 women will die from this disease[22].

Figure 4. Reproduced from Reference 21



GENERAL SUMMARY OF THE CLINICAL REPORT

The following summary is a general, lay audience summary of the medical records from UNC Health, provided to me by attorneys for the plaintiff, Jacqueline Tukes. I have reviewed the full report and have focused this summary on the information that, in my opinion, is the most relevant for the interpretation and assessment of the genetic testing results related to the patient's RCC.

The medical records demonstrate that Jacqueline Tukes, has a history of renal cell carcinoma, rhabdomyolysis, transient ischemic attacks (TIAs), and hypertension. This is in addition to other health concerns that, in my opinion, are less relevant to the RCC and the genetic testing results. The patient appears to have been 45 years old when she was originally diagnosed with RCC. A right partial nephrectomy was conducted in August 2010. Three additional areas of concern were subsequently identified (2 renal cysts and 1 small left renal lesion) and the patient underwent a left partial nephrectomy in April 2018. Based on a review of the records, the bilateral nature of the disease (in both kidneys), the relatively early onset of the disease in the patient, and a potential family history of RCC from the mother based on questionnaire responses resulted in her medical

team suspecting either a genetic (heritable) cause for the RCC or another underlying disease, specifically von Hippel-Lindau disease (VHL). These appear to be the underlying factors used as rationale to support the genetic testing. Additional concerns noted in the medical records refer to the family history that indicates an autosomal dominant transmission of rhabdomyolysis impacting multiple family members. This is unique as this disease is typically transmitted through an autosomal recessive mechanism. In terms of additional risk factors for RCC, it was also noted throughout the report that the patient was a "never smoker", was considered overweight, and it was noted that she had high blood pressure that appears to have been difficult to control.

GENETIC TESTING: INVITAE HEREDITARY RENAL/URINARY TRACT CANCERS PANEL

Genetic testing was conducted by Invitae with results initially reported in the medical records dated 08/08/2018. According to their website, Invitae is a biotechnology company that conducts genetic testing in support of oncology, women's health, pediatrics, rare diseases, cardiology, neurology, and proactive health. Invitae is a College of American Pathologists (CAP)-accredited and Clinical Laboratory Improvement Amendments (CLIA)-certified clinical diagnostic laboratory performing full-gene sequencing and deletion/duplication analysis using next-generation sequencing technology (NGS). The company was recently acquired by Labcorp to incorporate it's genetic testing technology with Labcorp's specialty testing capabilities. At the request of the patient's clinical team, blood was collected for genetic testing using the Invitae Renal/Urinary Tract Cancers Panel (current test code 01361). Based on information from Invitae, this panel analyzes genes associated with the predisposition to kidney and urinary tract cancers. The testing panel included assessments of 30 genes, shown in **Table 1**. The test panel run on the patient at the time included SDHA and SDHD, in place of BLM and REST on the currently offered primary panel. This panel tests for the disorders listed in **Tables 2[23] and Appendix A[24]**. Based on information provided by Invitae, the sequence analysis covers clinically important regions of each gene on the panel, including coding exons and 10 to 20 base pairs of adjacent intronic sequence on either side of the coding exons in the transcripts listed. In addition, the analysis covers select non-coding variants. Any variants that fall outside

Table 1: Primary Panel of Genes Assessed

BAP1	BUB1B	CDC73	CDKN1C
CEP57	DICER1	DIS3L2	EPCAM
FH	FLCN	GPC3	MET
MITF	MLH1	MSH2	MSH6
PALB2	PMS2	PTEN	SDHA
SDHB	SDHC	SDHD	SMARCA4
SMARCB1	TP53	TSC1	TSC2
VHL	WNT1		

these regions are not analyzed. Any limitations in the analysis of these genes will be listed on the report.

In the assay information provided by Invitae, based on validation study results, this assay achieves >99% analytical sensitivity and specificity for single nucleotide variants, insertions, and deletions <15bp in length, and exon-level deletions and duplications (**Table 3 and Appendix A**). Invitae's methods also detect insertions and deletions larger than 15bp but smaller than a full exon; however, sensitivity for these may be marginally reduced. Invitae's deletion/duplication analysis determines copy number at a single exon resolution at virtually all targeted exons. However, in rare situations, single-exon copy number events may not be analyzed due to inherent sequence properties or isolated reduction in data quality. Certain types of variants, such as structural rearrangements (e.g. inversions, gene conversion events, translocations, etc.) or variants embedded in sequence with complex architecture (e.g. short tandem repeats or segmental duplications), may not be detected. Additionally, it may not be possible to fully resolve certain details about variants, such as mosaicism, phasing, or mapping ambiguity. Unless explicitly guaranteed, sequence changes in the promoter, non-coding exons, and other non-coding regions are not covered by this assay. It is also noted that this report reflects the analysis of an extracted genomic DNA sample. In very rare cases, (circulating hematolymphoid neoplasm, bone marrow transplant, recent blood transfusion) the analyzed DNA may not represent the patient's constitutional genome. However, there is no indication that this is relevant to the patient in this case.

Table 2. Disorders Tested by Genetic Panel

1	BAP1 tumor predisposition syndrome
2	Beckwith-Wiedemann syndrome
3	Birt-Hogg-Dubé (BHD) syndrome
4	Bloom syndrome
5	CDC73-related conditions
6	Constitutional mismatch repair deficiency (CMMR-D)
7	DICER1-related pleuropulmonary blastoma familial tumor predisposition syndrome
8	FH tumor predisposition syndrome
9	Hereditary paraganglioma-pheochromocytoma syndrome
10	Li-Fraumeni syndrome
11	Lynch syndrome
12	MET-related hereditary papillary renal cell carcinoma (HPRCC)
13	Mosaic variegated aneuploidy syndrome
14	Perlman syndrome
15	PTEN hamartoma tumor syndrome (PHTS)
16	Rhabdoid tumor predisposition syndrome
17	Simpson-Golabi-Behmel syndrome (SGBS)
18	Small cell carcinoma of the ovary, hypercalcemic type
19	Tuberous sclerosis complex
20	Von Hippel-Lindau syndrome
21	Wilms tumor
22	WT1-related disorders

Table 3. Gene and Transcript References (reproduced from Reference 23 and clinical report)

Gene	Transcript reference	Sequencing analysis	Deletion/Duplication analysis
BAP1	NM_004656.3	yes	yes
BLM	NM_000057.3	yes	yes
BUB1B	NM_001211.5	yes	yes
CDC73	NM_024529.4	yes	yes
CDKN1C	NM_000076.2	yes	yes
CEP57*	NM_014679.4	yes	yes
CHEK2	NM_007194.3	yes	yes
CTR9	NM_014633.4	yes	yes
DICER1*	NM_177438.2	yes	yes
DIS3L2*	NM_152383.4	yes	yes
EPCAM*	NM_002354.2	yes	yes
FBXW7	NM_033632.3	yes	yes
FH*	NM_000143.3	yes	yes
FLCN	NM_144997.5	yes	yes
GPC3*	NM_004484.3	yes	yes
MAX*	NM_002382.4	yes	yes
MET*	NM_001127500.1	yes	yes
MITF	NM_000248.3	yes	yes
MLH1*	NM_000249.3	yes	yes
MSH2*	NM_000251.2	yes	yes
MSH6*	NM_000179.2	yes	yes
NYNRIN	NM_025081.3	yes	yes
PMS2*	NM_000535.5	yes	yes
PTEN*	NM_000314.4	yes	yes
REST	NM_005612.4	yes	yes
SDHA*	NM_004168.3	yes	no
SDHB	NM_003000.2	yes	yes
SDHC*	NM_003001.3	yes	yes
SDHD	NM_003002.3	yes	yes
SMARCA4	NM_001128849.1	yes	yes
SMARCB1	NM_003073.3	yes	yes
TMEM127	NM_017849.3	yes	yes
TP53*	NM_000546.5	yes	yes
TRIM28	NM_005762.3	yes	yes
TRIP13	NM_004237.4	yes	yes
TSC1*	NM_000368.4	yes	yes
TSC2	NM_000548.3	yes	yes
VHL	NM_000551.3	yes	yes
WT1	NM_024426.4	yes	yes

* CEP57: Sequencing analysis for exons 9 includes only cds +/- 10 bp.
* DICER1: Sequencing analysis for exons 22 includes only cds +/- 10 bp.
* DIS3L2: Deletion/duplication analysis is not offered for exon 19.
* EPCAM: Sequencing analysis is not offered for this gene.
* FH: Sequencing analysis for exons 9 includes only cds +/- 10 bp.
* GPC3: Sequencing analysis for exons 3 includes only cds +/- 10 bp.
* MAX: Sequencing analysis for exons 2 includes only cds +/- 10 bp.
* MET: Sequencing analysis for exons 12 includes only cds +/- 10 bp.
* MLH1: Deletion/duplication analysis covers the promoter region.
  Sequencing analysis for exons 12 includes only cds +/- 10 bp.
* MSH2: Analysis includes the exon 1-7 inversion (Boland mutation).
  Sequencing analysis for exons 2, 5 includes only cds +/- 10 bp.
  Deletions restricted to only the EPCAM gene will not be detected unless EPCAM analysis is requested.
* MSH6: Sequencing analysis for exons 7, 10 includes only cds +/- 10 bp.
* PMS2: Sequencing analysis for exons 7 includes only cds +/- 10 bp.
* PTEN: Sequencing analysis for exons 8 includes only cds +/- 10 bp.
* SDHA: Deletion/duplication analysis is not offered for this gene and sequencing analysis is not offered for exon 14. Sequencing analysis for exons 6-8 includes only cds +/- 10 bp.
* SDHC: Sequencing analysis for exons 2, 6 includes only cds +/- 10 bp.
* TP53: Deletion/duplication analysis covers the promoter region.
* TSC1: Sequencing analysis for exons 21 includes only cds +/- 10 bp.

TESTING METHODS

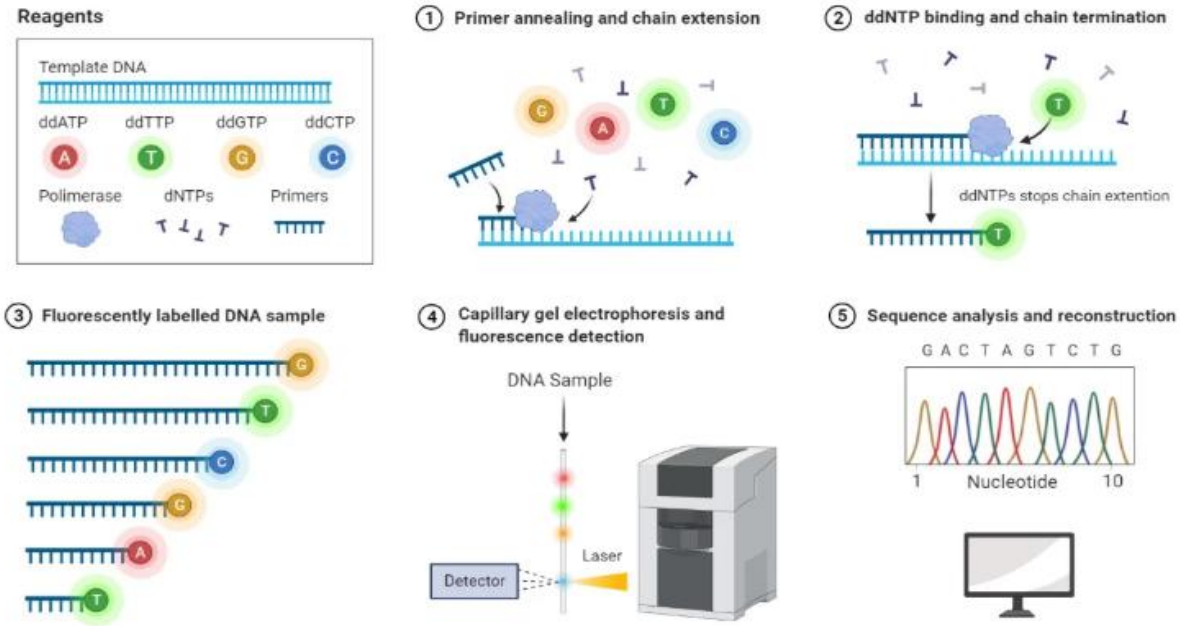
The following testing methods were reproduced and modified from the Clinical Report from sections dated 08/08/2018. Genomic DNA was obtained from the submitted samples, in this case blood from the patient, and was enriched for targeted regions using a hybridization-based protocol, and sequenced using Illumina Next-Generation Sequencing (NGS) technology. Unless otherwise indicated, all targeted regions were sequenced with >50x depth or were supplemented with additional analysis. Reads were aligned to a reference sequence (presumably GRCh37), and sequence changes were identified and interpreted in the context of a single clinically relevant transcript, indicated in **Table 3 and Appendix A**. Enrichment and analysis focused on the coding sequence of the indicated transcripts, 10bp of flanking intronic sequence (or 20bp for select evaluation of known cancer associated gene mutations) and other specific genomic regions demonstrated to be causative of the disease at the time of the assay design. Promoters, untranslated regions, and other non-coding regions were not otherwise interrogated. For some genes, only targeted loci were analyzed (indicated in **Table 3**). Exon deletions and duplications were called using an in-house algorithm at Invitae that determines copy number at each target by comparing the read depth for each target in the proband sequence with both mean read depth and read-depth distribution, obtained from a set of clinical samples. All clinically significant observations were confirmed by orthogonal technologies, except individually validated variants and variants previously confirmed in a first-degree relative. Confirmation technologies included

some version of any of the following: Sanger sequencing; Pacific Biosciences (PacBio) SMRT sequencing; Multiplex Ligation-Dependent Probe Amplification (MLPA), or Array Comparative Genomic Hybridization (Array CGH). These validation assays were performed if relevant to the requisition. General background information, strengths, and weaknesses of each technology are as follows:

- Illumina Next-Generation Sequencing (NGS): is a standard approach to identify clinically relevant gene mutations in patient samples. The technology is 99 – 99.9% accurate[25]. Benefits of the technology include ultra-high throughput, scalability, and speed. The technology is used to determine the order of nucleotides in the entire genome or in targeted regions of DNA (**Figure 5**). The technology utilizes sequencing by synthesis (SBS) chemistry, which tracks the addition of labeled nucleotides as the DNA chain is copied. Limitations of NGS include short read lengths (usually around 200-300 bases) and a relatively higher error rate (0.1-1%) compared to other technologies, especially in target regions with a high GC content[25] (NHS England; Illumina).
- Sanger sequencing: is a commonly used sequencing approach that is 99.9% accurate at calling bases. It is best used for disorders caused by a single, short gene. However, it is less effective in identifying deletions, duplications, or structural genome rearrangements[26].
- PacBio SMRT Sequencing: is a single-molecule real-time (SMRT) sequencing technology that can achieve up to 99.999% accuracy for genome assembly and genomic variant detection[27]. This approach is highly useful for long-range sequencing and is commonly used to validate or confirm results obtained with either Sanger sequencing and/or NGS.
- MLPA: is a technology that can readily detect deletions and duplications of genes and is highly efficient in detecting copy number variations and epigenetic modifications. When combined with NGS, it is also effective at determining single nucleotide variants. MLPA is a multiplex polymerase chain reaction (PCR) based assay that uses probes specific for different DNA sequences. This approach is commonly used to detect exon-level copy number variation (deletions or duplications) in specific genes. Balanced rearrangements, small changes in intronic DNA, and mosaicism can be difficult for MLPA to detect and commercial MLPA kits are not available for all genes[28].
- Array CGH: is a microarray-based technology used to detect small genetic changes in copy number and is commonly used in cancer cytogenomic studies. This technology can define the size, breakpoint, and gene content in clonal abnormalities. It offers high

resolution copy number variant detection. However, it is less effective in identifying small copy number changes in exons and changes within genes[29].

Figure 5. Next Generation Sequencing Overview



Of relevance to the current report, for PMS2 exons 12-15, the reference genome was modified to force all sequence reads derived from PMS2 and the PMS2CL pseudogene to align to PMS2 and variant calling algorithms were modified to support an expectation of 4 alleles. If a rare SNP or insertion/deletion variant was identified by the method, both PMS2 and the PMS2CL pseudogene were amplified by long-range PCR and the location of the variant was determined by PacBio SMRT sequencing of the relevant exon in both long-range amplicons. If a copy number variation (CNV) is identified, MLPA or MLPA-seq is run to confirm the variant. If confirmed, both PMS2 and PMS2CL are amplified by long-range PCR, and the identity of the fixed differences between PMS2 and PMS2CL are sequenced by PacBio from the long-range amplicon to disambiguate the location of the CNV. The technical components of the confirmatory sequencing was performed by Invitae Corporation. The methods section of the report concludes by defining PMID, rsID, and MedGen ID/OMIM number, which are reference numbers established in the National Library of Medicine for the scientific literature cited, gene identification, and variation identifications discussed in the report (**Appendix A**).

The report states assay specific limitations noted by Invitae. This assay achieves >99% sensitivity and specificity for single nucleotide variants, insertions, and deletions <15bp, based on the validation study results. Sensitivity to detect insertions and deletions larger than 15bp, but smaller than a full exon may be marginally reduced. Expansions and contractions within trinucleotide repeat regions may not be detected unless specified. Invitae's deletion/duplication analysis determines copy number with high confidence at >95% of targeted exons. The methodology utilized by Invitae may not detect low-level mosaicism. This report reflects the analysis of an extracted DNA sample. In very rare cases, the analyzed DNA may not represent the patient's constitutional genomes (i.e. following bone marrow transplant or recent blood transfusion). However, there is no indication this is relevant in the current case.

The report also has a disclaimer attached that states that DNA studies do not constitute a definitive test for the selected condition(s) in all individuals. It should be realized that there are possible sources of error. Errors can result from trace contamination, rare technical errors, rare genetic variants that interfere with the analysis, recent scientific developments, and alternative classification systems. The test should be one of many aspects used by the healthcare provider to help with a diagnosis and treatment plan, but it is not a diagnosis itself. This test was developed and its performance characteristics determined by Invitae. It has not been cleared or approved by the FDA. The laboratory is regulated under the Clinical Laboratory Improvement Act (CLIA) as qualified to perform high-complexity clinical tests. The test is used for clinical purposes. It should not be regarded as investigational or for research. The report was reviewed and approved by Dr. Matteo Vatta, Ph.D., FACMG, who is a Clinical Molecular Geneticist. FACMG refers to a Fellow, American College of Medical Genetics and Genomics.

GENETIC TESTING RESULTS

The findings of the report were "negative," meaning that the genetic testing did not reveal any pathogenic variants (genetic mutations) currently known to be associated with a genetic risk of renal cell carcinoma. The diagnostic test evaluated 30 genes listed in **Table 3** for genetic changes associated with increased risk of renal cell carcinoma and the additional diseases listed in **Table 2**. As stated in the report, results are negative unless otherwise indicated. Of the 30 genes evaluated, only two genetic variants were identified in the genes PMS2 and SMARCA4. These variants were defined as "Variants of Uncertain Significance" (VUS). VUS refers to genetic variations identified through testing where the impact on a person's health is unknown. There is not enough information in the scientific literature and genetic variation databases to determine if these variants increase the risk of developing RCC or have any clinical

consequence at the time of identification. In essence, there is insufficient research or data available to understand the effect of the variant and the impact of the variant on gene function. The finding of VUSs are common, occurring in almost 20% of genetic tests[30]. It was further noted that both of these variants were heterozygous, meaning that the patient has one gene/allele with the VUS and one gene/allele that is normal. The initial findings related to these VUSs classified these variants as “Uncertain Significance.” This was later updated to “likely benign.”

1) PMS2, Exon 14, c2395C>T (pArg799Trp), heterozygous. Likely Benign

The PMS2 gene encodes a protein that is essential in repairing damaged DNA. This protein fixes errors made when DNA is copied (DNA replication) in preparation for cell division. It is a key component of the DNA mismatch repair system. DNA mismatch repair is critical in detecting and repairing errors that occur during DNA replication and preventing mutations that can lead to cancer. The sequence change noted in the medical records is predicted to replace the amino acid arginine with tryptophan at codon 799 in the PMS2 protein. This arginine appears to be highly conserved in the protein and there is a moderate physicochemical difference between arginine and tryptophan. In my opinion, these changes are most likely to impact charge and hydrophobicity. Specifically, arginine is a positively charged amino acid, while tryptophan is neutral, which can significantly alter electrostatic (charge) interactions within a protein. Tryptophan is a hydrophobic amino acid, which could disrupt the hydrophobicity of the protein, which would be predicted to impact protein stability, folding, and function. In the summary provided by Invitae, this variant has been reported in individuals with suspected Lynch syndrome, breast and/or ovarian cancer, and pancreatic cancer, with references provided. The ClinVar entry for this variant was identified as Variation ID: 91340. Due to its critical role in DNA mismatch repair, an algorithm specifically designed for the PMS2 gene suggests that this missense change is likely to result in the deletion/inactivation of the protein[31], which is also noted in the Invitae Report. However, in the Invitae Report, it is stated that this has not been confirmed by published functional studies and its clinical significance is uncertain. This is a heterozygous mutation in the patient. This mutation was originally classified as “Uncertain Significance” in the original UNC Health report. However, follow up assessments by Invitae and presumably UNC Health reclassified the PMS2 variant as “Likely Benign”. The likely benign designation is typically defined in the field as a change in the DNA sequence that is unlikely to cause a disease based on the current scientific knowledge. It was stated in the report that this change in variant classification was made as a result in the re-review of the evidence in light of new variant interpretation guidelines and/or new information.

2) SMARCA4, Exon 30, c4211T>G (pVal1404Gly), heterozygous. Likely Benign

The SMARCA4 gene encodes a protein called BRG1, which functions in chromatin remodeling through formation of a multi-protein complex called SWI/SNF. This protein regulates gene activity. This gene is frequently mutated in a variety of human cancers, including ovarian and uterine cancers. The sequence change noted in the medical records predicts that a valine is replaced with a glycine at codon 1404 of the BRG1 protein. The valine residue is weakly conserved and there is a moderate physicochemical difference between valine and glycine. In my opinion, these changes are most likely to impact protein structure and polarity. Glycine has a very small side chain that consists of a single hydrogen atom; whereas, valine has a larger sidechain made of an isopropyl group. This makes valine more nonpolar compared to glycine, which may impact the overall polarity and protein folding properties. The algorithms employed by Invitae appear to have produced conflicting results regarding the functional effect of this missense mutation on the BRG1 protein, suggesting that this mutation could be either deleterious or benign. This variant is present in population databases, although it is very rare with an ExAC frequency of 0.01% (i.e. it appears in less than 1 out of 10,000 individuals in the Exome Aggregation Consortium (ExAC) database). The low frequency can be an indicator that this mutation is pathogenic in nature. However, this variant has not been reported in the literature in individuals with SMARCA4-related diseases. This variant has been reported in the ClinVar genomic variation database (Variation ID: 135256) at the NIH National Library of Medicine. Based on the ClinVar entry, this variation is likely benign for the cancers where the mutation has been observed (hereditary cancer-predisposing syndrome and rhabdoid tumor predisposition syndrome 2). This mutation was originally classified as “Uncertain Significance” in the original UNC Health report for the patient. However, follow up assessments by Invitae and presumably UNC Health reclassified the SMARCA4 variant as “Likely Benign”. The likely benign designation is typically defined in the field as a change in the DNA sequence that is unlikely to cause a disease based on the current scientific knowledge. It was stated in the report that this change in variant classification was made as a result in the re-review of the evidence in light of new variant interpretation guidelines and/or new information.

3. Von Hippel-Lindau Disease (VHL) Findings

Von Hippel-Lindau (VHL) disease is a rare condition caused by a genetic mutation that results in an increased risk of developing recurrent cysts and tumors in multiple organs over time. VHL is a known risk factor for inherited renal cell carcinoma. VHL is typically caused by an inherited mutation of the VHL gene, with about 80% of patients inheriting this mutation from a parent[32].

Based on the medical records from UNC Health, the clinical team considered the potential that the patient may have VHL. However, the VHL gene was included in the panel evaluated by Invitae (**Table 1**) and no mutations were noted. In addition to the Invitae assessment, the patient was also evaluated for VHL in a separate test conducted by Mayo Medical Labs. This report was not included in the UNC Health records. However, the UNC Health Records state that a VHL full gene analysis was conducted and the findings were negative.

4. Hereditary papillary renal cancer associated with germline pathogenetic variants in the MET gene

In addition to VHL, the clinical team also considered the potential that the patient had hereditary papillary renal cancer associated with germline pathogenetic variants in the MET gene. The MET gene encodes for a protein that functions as a receptor for hepatocyte growth factor. Patients with inherited mutations in the MET gene are at a higher risk of developing papillary renal cell carcinoma. However, the MET gene was included in the panel evaluated by Invitae (**Table 1**) and no mutations were noted.

DATA INTERPRETAION

The following opinions are based on my review of the medical records provided from UNC Health and a comprehensive analysis of scientific literature and studies publicly available in the National Library of Medicine and searchable through Pubmed. The search for “Inherited Renal Cell Carcinoma” resulted in 468 records; the search for “PMS2 heterozygous” resulted in 177 results; and the search SMARCA4 heterozygous” resulted in 53 results. All searches included research dating from 1975 – 2025. This search and review was conducted between January 4, 2025 and January 20, 2025. Multiple types of publications were recovered in this literature review, including Opinion, Perspective, Review, and Editorial publications that did not contain data and solely reflected author opinions that were not included in my analysis. All remaining studies were reviewed and factored into the opinions shown below. Additional studies that did not appear in the original searches, but were either referred to by analyzed studies or provide additional insight into the topic were included as necessary and are included in the reference section of this report. The literature review process used here is standard for my field and has been used by me in over 120 research publications and prior literature reviews throughout my career. I have also used this process in other litigation associated with providing reports and opinions related to the biological mechanisms associated with disease processes following exposure to environmental chemicals.

Negative Genetic Testing Results

The genetic testing did not reveal any pathogenic variants (genetic mutations) currently known to be associated with a genetic risk of renal cell carcinoma. This includes both inherited mutations and congenital mutations that are associated with the disease. Genetic variants have been identified as a cause of inherited cancer risk in some RCC-prone families. However, pathogenic variants have been estimated to account for only 5 - 8% of RCC cases overall[20]. The genetic testing for these RCC-associated genes were negative. In addition, the genetic testing was negative for VHL and MET gene associated renal diseases, which are both significant risk factors for RCC. In addition to the known pathogenic variants that directly impact inherited RCC risk, addition pathogenic variants in other non-RCC-associated genes have been reported, typically occurring in genes associated with DNA repair[20]. The rate of these pathogenic alterations ranges from 12.8 – 17.0%[20]. Based on the comprehensive literature review conducted to support my opinions, the panel of genes evaluated here (**Table 4**) represent the current extent of the scientific knowledge associated with inherited and known genetic risk factors for RCC. Likewise, in my opinion, this panel would be highly effective in evaluating the other 22 disorders listed in **Table 3**, which includes VHL and MET related cancers. While some of the clinical features of the patient's disease are consistent with an inherited nature, the genetic testing conducted does not support this. Thus, it is more likely than not that the patient's RCC is not directly associated with an inherited or congenital genetic mutation.

PMS2 Variant of Unknown Significance

The PMS2 mutation was determined to be a VUS and the Invitae analysis determined that this mutation is "likely benign". It is important to note that this is in the context of direct causation for the patient's RCC and the other diseases evaluated by this genetic testing panel (**Table 2**). In the ClinVar database and in the genetic testing report, it is noted that this variant has been reported in individuals with suspected Lynch syndrome, breast and/or ovarian cancer, and pancreatic cancer. It should also be noted that the heterozygous nature of this mutation is a major factor in the designation of the mutation as being likely benign. Basically, the patient has one functioning copy of the gene PMS2 and one likely non-functional copy of the PMS2 gene, as this mutation is predicted to be deleterious (i.e. loss of function). A review of the ClinVar database does reveal that there is sufficient evidence for dosage pathogenicity for the PMS2 gene and this is currently under review. Dosage pathogenicity or haploinsufficiency, is a condition whereby

having a single functional copy of a gene, such as seen here in the patient, is insufficient to maintain normal function[33].

The protein encoded by the PMS2 gene (Gene ID 5395) is a key component of the mismatch repair system that functions to correct DNA mismatches, small mutational insertions, and small mutational deletions that can occur during DNA replication and homologous recombination. Specifically, this protein functions with the gene product of the mutL homolog 1 (MLH1) gene to form heterodimers that recognize and repair mismatched DNA. Loss of function of this system significantly impairs a cell's ability to fix damaged DNA and results in an individual that is more sensitive to cancer following the induction of DNA mismatches. As discussed above, genetic instability and mutation is considered an enabling characteristic of cancer (**Figure 3**). This increased sensitivity to cancer, has been observed in defined pathogenic variants in DNA mismatch repair genes, such as MLH1, MSH2, PMS2, and MSH6, which are associated with a variety of human malignancies[34]. This is especially true in the context of increased genotoxicity and/or exposure to agents that induce DNA damage. For example, this has been observed in pre-clinical rodent models using animals that are heterozygous for PMS2[35], which is similar to the heterozygous status of the patient in this case, where the animals have 1 functional copy of PMS2 and 1 non-functional copy of PMS2. The heterozygous mice do not develop spontaneous tumors, suggesting that they have sufficient mismatch repair function to prevent normally occurring genomic instability driven by their one good copy of PMS2. However, when these animals are exposed to exogenous carcinogens, this overloads the lower capacity for mismatch repair, resulting in an increased rate of tumor production[35]. When these mice were exposed to N-methyl-N-nitrosourea (MNU), which is a known carcinogen that damages DNA, the animals were significantly more likely to develop intestinal tumors, both adenomas and adenocarcinomas after the MNU treatment compared to mice with the two normal copies of PMS2[35]. This effect was determined to be organ/tissue/cancer specific as there were no differences in the incidence of thymic lymphomas, which are common following MNU treatment, between the heterozygous and normal PMS2 mice[35]. Thus, while it is not likely that the PMS2 mutation observed in the patient directly contributes to RCC and is likely benign in this context, there is compelling evidence that indicates dosage pathogenicity. In my opinion, based on the function of PMS2 as a tumor suppressor, the predicted loss of function mutation observed in the patient, the "sufficient evidence for dosage pathogenicity" haploinsufficiency score (HI score) in the ClinVar database, and the data related to carcinogen exposure in heterozygous animal models, it is as likely as not that this mutation results in insufficient DNA mismatch repair in the patient. As observed in the

animal studies, this would be expected to result in increased cancer presentation following carcinogen exposure and greater sensitivity to carcinogens, specifically those that damage DNA.

SMARCA4 Variant of Unknown Significance

The SMARCA4 mutation was determined to be a VUS and the Invitae analysis determined that this mutation is "likely benign". As with PMS2, it is important to note that this is in the context of direct causation for the patient's RCC and the other diseases evaluated by this genetic testing panel (**Table 2**). In the ClinVar database and in the genetic testing report, it is noted that this variant has been reported in individuals with Rhabdoid tumor predisposition syndrome 2 and hereditary cancer-predisposing syndrome. It should also be noted that the heterozygous nature of this mutation is a major factor in the designation of the mutation as being likely benign. A review of the ClinVar database does reveal that there is "sufficient evidence for dosage pathogenicity" (HI score) for the SMARCA4 gene that has been "confirmed". For this gene, having a single functional copy is insufficient to maintain normal function. However, the algorithms employed by Invitae appear to have produced conflicting results regarding the functional effect of the missense mutation on the BRG1 protein that is encoded by the SMARCA4 gene, suggesting that this mutation could be either deleterious or benign. The protein encoded by this gene (Gene ID: 6597) functions in the regulation of gene transcription, which contributes either directly or indirectly to all the Hallmarks of cancer discussed previously in this report (**Figure 3**). It has also been shown that this protein can bind to the tumor suppressor BRCA1 and can regulate the expression of the tumorigenic protein CD44. In studies using targeted knockout of BRG1 (SMARCA4), heterozygous loss of BRG1 resulted in an increased number and size of lung tumors following exposure to ethyl carbamate, which is a lung carcinogen, compared to tumors observed in animals with both functional pairs of SMARCA4[36]. When both copies of BRG1 were inactivated, which would be a complete loss of function or homozygous deletion, there was no difference in lung tumor formation compared to the control animals[36]. In the complete absence of all functional BRG1, the cells appear to undergo controlled cell death before becoming cancerous. Loss of function of BRG1 also increased tumor development following exposure to ethyl carbamate, which is another carcinogen that was used in this study[36]. It was also noted that inactivation of BRG1 could not, by itself, initiate tumor development in untransformed cells; thus, requiring carcinogen exposure to initiate the cancer development[36]. Based on the function of SMARCA4 (BRG1) and the experimental data related to heterozygous loss of BRG1, <u>if the mutation carried by the patient has a deleterious effect on the protein, then it is as likely as not that this mutation results in increased cancer development following exposure to carcinogens.</u>

SUMMARY OF FINDINGS AND KEY OPINIONS

In my opinion, the cumulative findings from the genetic testing demonstrates that it is more likely than not that the patient's RCC is not directly caused by an inherited or congenital genetic mutation. This is based on the lack of pathogenic mutations/variations in genes currently known to be causative for RCC and tested in this genetic screening panel. The patient is also negative for the other diseases evaluated by this genetic screening panel, which includes diseases such as VHL that are known to be causative for RCC. The two variants of unknown significance in the PMS2 gene and the SMARCA4 gene are likely benign for the direct causation of RCC. The literature indicates that heterozygous changes in these genes do not increase the sporadic occurrence of specific cancers; rather, they require carcinogen exposure to initiate the cancer development. Thus, it is as likely as not that these mutations contribute to an increase in the patient's overall cancer development following exposure to carcinogens and susceptibility to carcinogens, at doses that would not ordinarily lead to increased tumor development in individuals without these mutations. PMS2 and SMARCA4 function through two distinct mechanisms, that when dysregulated contribute to cancer. For the heterozygous PMS2 variant in the patient, which is predicted to be a deletion mutation, only having one functional copy of the PMS2 gene/protein is expected to result in increased cancer presentation following exposure to carcinogens, specifically those that damage DNA. This is due to the loss of optimized DNA mismatch repair – i.e. damaged DNA cannot be effectively repaired resulting in the accumulation of mutations in cells and ultimately leading to the acquisition of multiple cancer hallmarks. For the heterozygous SMARCA4 variant, if the mutation carried by the patient has a deleterious effect on the protein, only having one functional copy of the SMARCA4 gene/protein is expected to result in increased cancer development following exposure to carcinogens by disrupting chromatin remodeling. Dysfunctional SMARCA4 alters the regulation of gene transcription leading to uncontrolled cell growth and differentiation – i.e. cells can no longer properly read and access important genes to control their proliferation and behavior leading to the acquisition of multiple cancer hallmarks.

DISCLOSURES

All the opinions expressed in this report are my own, are based on my training and expertise in molecular biology and cancer biology and were provided in my capacity as President of Allen Consulting and Management, LLC. While I am also employed by Virginia Polytechnic Institute and State University (Virginia Tech), this work was conducted independently from my position at this

University. The content of this report is the responsibility of the author, and does not necessarily represent the official views of Virginia Tech or any funding agencies that support my academic research program. My opinions are based on my evaluation of the medical records of Jacqueline Tukes, the peer-reviewed scientific literature, and the other sources noted in reference section of this report. I reserve the right to supplement these opinions if new information, data, and/or evidence becomes available and to address the opinions and/or testimony of other parties that reference the opinions expressed in this report. I have provided expert testimony in other court proceedings related to environmental exposures to chemicals and cancer. I am being compensated for my time generating this report at a rate of $400 per hour.

Dr. Irving C. Allen
President and Managing Partner
Allen Consulting and Management, LLC

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Appendix A. Invitae Hereditary Renal/Urinary Tract Cancers Panel: Disorders Tested

INVITAE

Invitae Hereditary Renal/Urinary Tract Cancers Panel: Disorders Tested

The Invitae Hereditary Renal/Urinary Tract Cancers Panel analyzes genes that are associated with predisposition to renal cancer and cancer of the urinary tract including but not limited to Birt-Hogg-Dubé (BHD) syndrome, FH tumor predisposition syndrome, and von Hippel-Lindau syndrome. These genes were selected based on the available evidence to date to provide a broad panel for hereditary renal/urinary tract cancer. Heritable predisposition to this cancer type is genetically heterogeneous, and broad panel testing allows for an efficient evaluation of many potentially relevant genes based on a single clinical indication.

Disorders Tested	Disorder Description	PMID	Gene
BAP1 tumor predisposition syndrome	BAP1 tumor predisposition syndrome is associated with an increased risk for cutaneous and uveal melanoma, malignant pleural mesothelioma and renal cell carcinoma; lifetime cancer risks are unclear. BAP1 tumor predisposition syndrome has an autosomal dominant inheritance pattern.	22935333, 23684012	BAP1
Bloom syndrome	Bloom syndrome is characterized by proportionate small stature, microcephaly, abnormal skin pigmentation, facial anomalies, sun-sensitive facial erythema, infertility, immunodeficiency, and a predisposition to a wide variety of cancers. Bloom syndrome has an autosomal recessive inheritance pattern.	16763388, 5770175	BLM
Mosaic variegated aneuploidy syndrome	MVA syndrome is a rare condition associated with mosaic aneuploidies involving multiple different chromosomes and tissues. Clinical features include intrauterine growth restriction, microcephaly, eye anomalies, dysmorphic features and neurologic pathology. While BUB1B-associated MVA is associated with various malignancies including Wilms tumor, rhabdomyosarcoma and leukemia, cancer has not been described among the few reported cases of CEP57- and TRIP13-associated MVA; therefore, this association is uncertain. MVA has an autosomal recessive inheritance pattern.	10429359, 18548531, 35434947, 28553959	BUB1B CEP57 TRIP13
CDC73-related conditions (hyperparathyroidism-jaw tumor syndrome (HPT-JT), parathyroid carcinoma, and familial isolated hyperparathyroidism (FIH))	CDC73-related conditions are a clinical spectrum inclusive of familial isolated hyperparathyroidism (FIHP), parathyroid carcinoma, and hyperparathyroidism-jaw tumor (HPT-JT) syndrome. While FIHP and hereditary parathyroid carcinoma lack additional extra-organ involvement, HPT-JT is typically a multi-systemic neoplastic condition. Features include primary hyperparathyroidism due to parathyroid adenoma or carcinoma, ossifying fibroma(s) of the maxilla and/or mandible, and renal lesions including cysts, hamartomas and Wilms' tumor. CDC73-related conditions have an autosomal dominant inheritance pattern.	16720667, 20301744	CDC73
Beckwith-Wiedemann syndrome	Beckwith-Wiedemann syndrome is an autosomal dominant overgrowth disorder characterized by macrosomia, macroglossia, visceromegaly, hemihyperplasia, omphalocele, neonatal hypoglycemia, and renal abnormalities. There is an increased risk for neoplasia, particularly Wilms tumor, hepatoblastoma, neuroblastoma, adrenocortical carcinoma and rhabdomyosarcoma; these risks are highest in the newborn period through eight years of age.	24335096, 24911853, 20301568	CDKN1C
DICER1-related pleuropulmonary blastoma familial tumor predisposition syndrome	DICER1-related pleuropulmonary blastoma familial tumor predisposition syndrome is an autosomal dominant condition associated with an increased risk for ovarian sex cord-stromal tumors, pleuropulmonary blastoma, cystic nephroma and thyroid neoplasia including goiter, adenoma and differentiated thyroid cancer.	19556464, 21205968, 21266384, 25451712	DICER1
Perlman syndrome	Perlman syndrome is an overgrowth disorder characterized by macrosomia, renal dysplasia, nephroblastomatosis and Wilms tumor. Affected infants have a high rate of neonatal morbidity; the incidence of Wilms tumor in those who survive the neonatal period has been estimated at 64%. Perlman syndrome has an autosomal recessive inheritance pattern.	23613427, 18780370	DIS3L2
Lynch syndrome	Lynch syndrome, also called hereditary non-polyposis colon cancer (HNPCC), increases the risk of many types of cancer, particularly colorectal. Other associated cancers include stomach, small bowel, kidney, central nervous system, biliary tract, pancreatic, prostate, and skin. Women with this disorder also have an increased risk for ovarian and uterine cancer. Lynch syndrome is the most common cause of adult-onset hereditary colorectal and uterine cancers. Lynch syndrome has an autosomal dominant inheritance pattern.	21642682, 28754778, 19900449, 26657901, 31337882, 23091106, 18398828, 27013479	MLH1 MSH2 MSH6 PMS2 EPCAM
Constitutional mismatch repair deficiency (CMMR-D)	CMMR-D is an autosomal-recessive cancer syndrome characterized by childhood malignancies, most commonly hematological malignancies and/or brain tumors, as well as very early-onset colorectal cancer. Almost all individuals also show some signs reminiscent of neurofibromatosis type 1 (NF1), such as café-au-lait spots. CMMR-D has an autosomal recessive inheritance pattern.	18709565, 20442441, 17539897	MLH1 MSH2 MSH6 PMS2
FH tumor predisposition syndrome	FH tumor predisposition syndrome is characterized by cutaneous leiomyomas, early onset uterine leiomyomas, kidney tumors, and kidney cancer. Uterine leiomyomas, also known as fibroids, are present in nearly all affected females. The lifetime risk for renal cell carcinoma is approximately 21%. Malignant transformation of cutaneous leiomyomas has also been described. Some individuals with a clinically significant change in FH may also develop paragangliomas (PGL) and pheochromocytomas (PCC). PGL are nervous system tumors that often form in the head, neck, spine, and abdomen. PCC are adrenal gland tumors that may cause symptoms including tachycardia and hypertension. Most PGL and PCC are benign, and while there is malignant potential, lifetime cancer risks are unclear. FH tumor predisposition syndrome has an autosomal dominant inheritance pattern.	20301430, 31831373, 28300276	FH
Birt-Hogg-Dubé (BHD) syndrome	BHD syndrome is an autosomal dominant condition characterized by an increased risk to develop noncancerous cysts in the lungs and kidneys in addition to acrochordons, fibrofolliculomas and trichodiscomas on the face, neck, and upper body. There is a risk of developing one or more spontaneous pneumothorax. Affected individuals also have an increased risk of kidney cancer; however, lifetime risks are not established.	25519092 , 25519458, 18234728	FLCN
Simpson-Golabi-Behmel syndrome (SGBS)	SGBS is characterized by pre- and postnatal overgrowth, characteristic facial features and visceromegaly. Clinical features include cleft lip or palate, heart defects, and anomalies of the skeleton, kidneys, and genitourinary system. SGBS is associated with an increased risk of Wilms tumor and other embryonal tumors such as hepatoblastoma, adrenal neuroblastoma, gonadoblastoma, and hepatocellular carcinoma. Craniosynostosis has been reported in rare cases. All males are expected to have features of SGBS; however, there is variability in the clinical severity. SGBS has an X-linked inheritance pattern; females are frequently unaffected but may also have clinical features of SGBS due to skewed X-inactivation.	24115482, 19372699, 25238977	GPC3
MET-related hereditary papillary renal cell carcinoma (HPRCC)	The MET gene is associated with autosomal dominant predisposition to hereditary papillary renal cell carcinoma (HPRCC). HPRCC is a rare, highly penetrant hereditary cancer syndrome characterized by an increased lifetime risk of developing type 1 papillary renal cell carcinoma (PRCC). These tumors are typically multifocal and bilateral.	24710684, 9563489, 12647800, 8308957	MET
PTEN hamartoma tumor syndrome (PHTS)	PTEN hamartoma tumor syndrome is a highly variable hamartomatous condition characterized by macrocephaly, Lhermitte-Duclos disease, mucocutaneous lesions, gastrointestinal hamartomas, lipomas, benign thyroid lesions, macular pigmentation of the glans penis, cerebrovascular malformations and several cancer types. Associated cancers include breast, thyroid (typically follicular), renal, endometrial, colorectal, and melanoma. PHTS is also associated with developmental delay, intellectual disability and autism spectrum disorder, and has an autosomal dominant inheritance pattern.	20301661, 22252256, 20565722, 24136893	PTEN
Hereditary paraganglioma-pheochromocytoma syndrome	Hereditary paraganglioma-pheochromocytoma syndrome (PGL-PCC) is a rare condition characterized by the development of rare, adult-onset neuroendocrine tumors that arise from paraganglia in the head and neck. Pheochromocytomas are a type of paraganglioma that most commonly develop in the adrenal glands and may cause excessive production of adrenal hormones, resulting in hypertension, headaches, anxiety, tachycardia, and sweaty or clammy skin. Some affected individuals may develop gastrointestinal stromal tumors (GIST) in addition to paragangliomas, a condition known as Carney-Stratakis syndrome. Hereditary paraganglioma-pheochromocytoma syndrome has an autosomal dominant inheritance pattern.	20301715	SDHB SDHC

APPENDIX B

CURRICULUM VITAE

Dr. Irving Coy Allen, MBA, PhD

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Google Scholar h-index: 50

CURRENT POSITIONS

2019 – present President, Allen Consulting and Management LLC, Blacksburg, Virginia

2019 – present President, Home by the Sea LLC, Blacksburg, Virginia

2023 - present Professor, Department of Biomedical Sciences and Pathobiology, Virginia-Maryland College of Veterinary Medicine Virginia Tech (tenured)

2024 – present Professor, Department of Basic Science Education, Virginia Tech Carilion School of Medicine

EDUCATION

1993 - 1997 Bachelor of Science in Biology, Concentration: Molecular Biology and Biotechnology, East Carolina University

1998 – 2000 Master of Science in Biology, The University of North Carolina at Greensboro

2002 – 2006 Doctor of Philosophy in Genetics and Molecular Biology, The University of North Carolina at Chapel Hill

2010 – 2012 Master of Business Administration, Concentration: Biosciences Management, North Carolina State University

PROFESSIONAL EXPERIENCE

1997 – 2001 Laboratory Technologist, Laboratory Corporation of America, Paternity Testing Division

1998 - 2000 Graduate Student, Laboratory of Dr. Parke Rublee, Department of Biology, The University of North Carolina at Greensboro.

2001 - 2002 Molecular Biology Laboratory Technologist, Center for Applied Aquatic Ecology, North Carolina State University (part time)

2001 - 2002 Research Analyst, Center for Human Genetics, Duke University Medical Center

2002 - 2006 Graduate Student, Laboratory of Dr. Beverly H. Koller, Curriculum in Genetics and Molecular Biology, The University of North Carolina at Chapel Hill

2007 - 2011 Postdoctoral Fellow, Laboratory of Dr. Jenny P.Y. Ting, Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill

2011 - 2012 Research Associate/Research Assistant Professor, Laboratory of Dr. Jenny P.Y. Ting, Department of Microbiology and Immunology, The University of North Carolina at Chapel Hill.

2012 – 2019 Assistant Professor of Inflammatory Diseases, Department of Biomedical Sciences and Pathobiology, Virginia-Maryland College of Veterinary Medicine, Virginia Tech

2014 – 2019 Assistant Professor of Health Sciences, Translational Biology, Medicine, and Health Program, Virginia Tech

2017 - 2021 Assistant Professor, Department of Basic Science Education, Virginia Tech Carilion School of Medicine, Virginia Tech
2019 - 2023 Associate Professor of Inflammatory Diseases, Department of Biomedical Sciences and Pathobiology, Virginia-Maryland College of Veterinary Medicine Virginia Tech
2021 - 2024 Associate Professor, Department of Basic Science Education, Virginia Tech Carilion School of Medicine, Virginia Tech

LEADERSHIP POSITIONS

PROFESSIONAL

2015 – 2020 Chair, Society for Mucosal Immunology Communications Committee
2017 - present Organizing Committee Member for the Southeastern Immunology Symposium
2018 - 2020 Board of Councilors, Society for Mucosal Immunology
2018 - 2022 Chair, Society for Leukocyte Biology Professional Development Committee
2019 Organizer and Co-Chair, 2019 IRE Immuno-Oncology Summit, April 15-17th, Blacksburg, VA
2019 International Scientific Advisory Committee Member, for the 19th International Congress of Mucosal Immunology
2020 – 2024 Section Editor, *The Journal of Immunology*
2020 – 2026 Deputy Editor, *The Journal of Leukocyte Biology*
2021 Scientific Advisory Board Member, integrated Translational Health Research Institute of Virginia (iTHRIV)
2021 - 2024 AAALAC, Board of Delegates Member
2022 Co-Chair, Society for Leukocyte Biology/Journal of Leukocyte Biology Methods Task Force
2024 – 2026 Panel Chair, Research Foundation Flanders (FWO), Med 4 Cancer Research
2024 – 2025 Vice Chair/Chair Elect, Pilot Grant Review Committee of Atrium Health Wake Forest Comprehensive Cancer Center

INDUSTRY ADVISORY BOARDS AND SERVICE:

2019 – 2021 IRE-Immuno Oncology Medical Advisory Board Member, AngioDynamics
2020 – present Scientific Advisory Board Member, MANA MEDTECH, LLC
2022 – present Scientific Advisory Board Member, DUB Biologics

UNIVERSITY

2019 – 2024 Member, Commission on Graduate and Professional Studies and Policies
2021 – 2023 Chair, Virginia Tech Graduate Curriculum Committee
2021 – 2024 Steering Committee Member, Virginia Tech Center for Drug Discovery
2024 - present Advisory Committee Member, Virginia Tech/Focused Ultrasound Foundation Center of Excellence
2024 - 2025 Provost's Leadership Development Program, Leading in Place, Virginia Tech, Blacksburg, VA

COLLEGE

2016 Steering Committee Member, Integrated Microbiology Program
2020 – 2024 Co-Chair, Center for Emerging, Zoonotic and Arthropod-borne Pathogens (CEZAP), Infectious Disease Immunology Focus Area
2023 – 2025 Chair, Research Committee, VMCVM
2024 – 2025 Member, VMCVM Strategic Planning Steering Committee

DEPARTMENT

October 2022-present — Assistant Department Head, Department of Biomedical Sciences and Pathobiology, Virginia-Maryland College of Veterinary Medicine Virginia Tech

ACADEMIC AND PROFESSIONAL HONORS

2000 The University of North Carolina at Greensboro University Excellence Award
2009 UNC Chapel Hill Graduate Education Advancement Board Impact Award
2009 UNC Chapel Hill Postdoctoral Award for Research Excellence
2009 NIH Individual National Research Service Award
2010 Lineberger Comprehensive Cancer Center Joseph S. Pagano Award
2010 American Cancer Society Postdoctoral Fellowship
2011 NIH K01 Career Development Award
2014 The 2014 Chambers-eBioscience Memorial Award, The American Association of Immunologists
2014 Travel for Techniques Award, The American Association of Immunologists
2020 Virginia Tech Outstanding Mentor Award

CURRENT AND PAST PROFESSIONAL AFFILIATIONS AND MEMBERSHIPS

2009 – present Member of the American Association for the Advancement of Science
2009 – present Member of the American Association of Immunologists
2012 – 2021 Member of the Society for Mucosal Immunology
2013 – 2016 Member of the Virginia Academy of Science
2014 – present Member of the American Society for Microbiology
2014 – present Member of the Society for Leukocyte Biology
2018 – present Member of the American Association for Cancer Research
2019 – 2022 Member of Sigma Xi

EDITORIAL RESPONSIBILITIES

EDITORIAL BOARDS:

2013 - 2015 Academic Editor: *PLoS One*
2015 - 2019 Associate Editor: *The Journal of Immunology*
2015 - 2019 Section Editor: *PLoS One*
2015 – 2016 Guest Editor: *Mediators of Inflammation*, Special Issue: “Holding the Inflammatory System in Check: TLRs and NLRs”
2016 - 2019 Review Editor: *Frontiers in Cellular and Infection Microbiology*
2018 - 2019 Review Editor: *Frontiers in Immunology*
2019 Invited Editor: *mBIO*
2019 - 2021 Associate Editor: *Frontiers in Immunology*
2019 – 2021 Associate Editor: *Frontiers in Microbiology*

***AD HOC* REVIEWER (selected):** *Science, PNAS; Mucosal Immunology; Nature Communications; Scientific Reports; Gut; Clinical Cancer Research; The Journal of Immunology; Inflammatory Bowel Diseases; Journal of Leukocyte Biology; Oncogene; Biomaterials; Journal of Virology; mBIO; mSphere; The FASEB Journal; Cellular and Molecular Life Sciences; American Journal of Physiology-Lung Cellular and Molecular Physiology; American Journal of Physiology-Heart and Circulatory Physiology; Clinical and Translational Medicine; Clinical and Experimental Gastroenterology; Clinical and Vaccine Immunology; BMC Immunology; Molecular Biology Reports; Cytokine; Inflammation Research; Immunology Letters*

TEXTBOOK REVIEWS:

1. Fowler, S., Roush, R., and Wise, J. (2013). *Concepts of Biology*,OpenStax College, Houston, Texas: Rice University Press
2. Avissar, Choi, DeSaix, Jurukovski, Wise, and Rye. (2013). *Biology*, OpenStax College, Houston, Texas: Rice University Press.

COMMITTEE AND LEADERSHIP SERVICE

STUDY SECTION SERVICE

2015	Austrian Science Fund, *Ad Hoc* Reviewer
2015	National Science Foundation, Grant Review Panel: Graduate Research Fellowship Program
2015	European Research Council (ERC) Consolidator Grant, *Ad Hoc* Step 2 Evaluator
2015	Swiss National Science Foundation, Division of Biology and Medicine, *Ad Hoc* Reviewer
2016	Austrian Science Fund, *Ad Hoc* Reviewer
2016	National Institutes of Health, Tumor Microenvironment (TME) Study Section Oncology 1, Basic Translational Integrated Review Group
2016	Swiss National Science Foundation, Division of Biology and Medicine, *Ad Hoc* Reviewer
2017	Austrian Academy of Sciences, *Ad Hoc* Reviewer
2018 - 2021	National Science Foundation, Grant Review Panel: Graduate Research Fellowship Program
2018	National Institutes of Health, Special Emphasis Panel, Center for Scientific Review, Program Evaluation of NIH Peer Review Processes
2018	Swiss National Science Foundation, Division of Biology and Medicine, *Ad Hoc* Reviewer
2018	Israel Science Foundation, Joint NSFC-ISF Research Grant, *Ad Hoc* Reviewer
2019	European Science Foundation, FWO Postdoctoral Fellowship Application Review, *Ad Hoc* Reviewer
2019	27th TV3 Marató on Cancer, Agency for Health Quality and Assessment of Catalonia, *Ad Hoc* Reviewer
2019	Swiss National Science Foundation, Division of Biology and Medicine, *Ad Hoc* Reviewer
2020 – 2023	Research Foundation Flanders (FWO), Med 4 Project Panel on Cancer Research, **Standing Panel Member**
2020	United Kingdom Medical Research Council, *Ad Hoc* Reviewer
2020	National Institutes of Health, SARS-CoV-2 Serological Sciences Centers of Excellence (U54) Special Emphasis Panel
2020	National Institutes of Health, Small Business: Cardiovascular and Surgical Devices Study Section
2020	National Institutes of Health, NIAID SARS-CoV-2/COVID-19 Emergency Funding Special Emphasis Panel
2021	National Institutes of Health, Small Business: Cardiovascular and Surgical Devices Study Section
2021	National Science Foundation, Engineering of Biomedical Systems (EBMS) Panel
2021	National Institutes of Health, Small Business: Cardiovascular and Surgical Devices Study Section

2021 United States Department of Veterans Affairs, Infectious Diseases A (INFA) Peer Review Panel
2021 National Institutes of Health, Innate Immunity and Inflammation (III) Study Section
2021 National Institutes of Health, NIAID Investigator Initiated Program Project Applications (P01) Study Section
2021 National Institutes of Health, NIAID Investigator Initiated Program Project Applications (P01) Study Section
2021 National Institutes of Health, Small Business: Cardiovascular and Surgical Devices Study Section
2021 National Institutes of Health, Innate Immunity and Inflammation (III) Study Section
2021 United States Department of Veterans Affairs, Infectious Diseases A (INFA) Peer Review Panel
2022 National Science Foundation, FY22 Engineering of Biomedical Systems (EBMS) UNS B Panel
2022 National Institutes of Health, Small Business: Cardiovascular and Surgical Devices Study Section
2022 National Institutes of Health, NIAID Investigator Initiated Program Project Applications (P01) Study Section
2022 United States Department of Veterans Affairs, Infectious Diseases A (INFA) Peer Review Panel
2022 National Institutes of Health, NCI Investigator Initiated Program Project (P01) SEP-2 Study Section
2022 National Institutes of Health, Small Business: Cardiovascular and Surgical Devices Study Section
2022-2024 United States Department of Veterans Affairs, Infectious Diseases-A Subcommittee
2023-2026 Research Foundation Flanders (FWO), Med 4 Cancer Research, **Standing Panel Member**
2023 National Institutes of Health, Innate Immunity and Inflammation (III) Study Section
2023 National Institutes of Health, Image Guided Interventions and Surgery (IGIS) Study Section
2023 The French National Cancer Institute (INCa), Biological and Basic Sciences for Cancer Research 2023 Review Panel, *Ad Hoc* Reviewer
2023 National Institutes of Health, Innate Immunity and Inflammation (III) Study Section
2023 National Institutes of Health, Drug and Biologic Therapeutic Delivery (DBTD) Study Section
2024 National Institutes of Health, Therapeutic Immune Regulation (TIR) Study Section
2024 National Institutes of Health, NIH/NIAID Support for Conferences and Scientific Meetings Study Section

GRANT REVIEW COMMITTEES:

2014 Biomedical and Health Science Peer –Review Panel, Virginia Tech Institute for Critical Technology and Applied Science (ICTAS) Transformative Science and Technology Seed Proposals

2015 Academia Sinica (Tiawan), First Round Grant Reviewer of 2016 Applications of the Thematic Research Program

2016 Engineered Health Junior Faculty Collaborative (JFC) Grant Panel, Virginia Tech Institute for Critical Technology and Applied Science (ICTAS)

2016 Center for Veterinary Regenerative Medicine (CVRM), Wake Forest Institute for Regenerative Medicine and Virginia Maryland College of Veterinary Medicine Seed Grant Program

2016 SEEDS: Ohio Agricultural Research and Development Center Research Enhancement Competitive Grants Program, The Ohio State University, *Ad Hoc* Reviewer

2017 Alzheimer's Association Research Grant Program, *Ad Hoc* Reviewer

2018 UK DogsTrust (formally the National Canine Defense League), Canine Welfare Grant, *Ad Hoc* Reviewer

2019 UK DogsTrust (formally the National Canine Defense League), Canine Welfare Grant, *Ad Hoc* Reviewer

2019 - 2022 Crohn's and Colitis Foundation, Research Fellowship Awards Committee, **Standing Panel Member**

2020 Cures Within Reach, *Ad Hoc* Reviewer

2020; 2024 Mitacs Accelerate Proposal (Canada), *Ad Hoc* Reviewer

2021 The Wellcome Trust-DBT India Alliance. *Ad Hoc* Reviewer

2021 - 2022 iTHRIV Scholar Program. *Ad Hoc* Reviewer

2022 Focused Ultrasound Foundation. *Ad Hoc* Reviewer

2023 – 2026 Pilot Grant Review Committee of Atrium Health Wake Forest Comprehensive Cancer Center. **Standing Panel Member**

2023 The Wellcome Trust. *Ad Hoc* Reviewer

2023 Rita Allen Foundation Scholar Award Selection Committee. VT Nomination. *Ad Hoc* Reviewer

2024 University of Padova (Italy), Department of Biology, Internal Grant Program. *Ad Hoc* Reviewer

2024 Pancreatic Cancer UK, Interdisciplinary Treatment Grant 2024/2025. *Ad Hoc* Reviewer

PROFESSIONAL SERVICE:

2013 – 2015 Member, Society for Mucosal Immunology Website Committee

2013 – 2016 Member, Virginia Academy of Science Publications Committee

2013 – 2016 Member, Virginia Academy of Science Archives Committee

2014 Panelist, AAAS USA Science and Engineering Festival

2014 – 2017 Member, Society for Leukocyte Biology Development Committee

2015 Reviewer, 17th International Congress of Mucosal Immunology, Subject Area Abstract Reviewer for Travel Awards and Programming

2015 Member, Virginia Velocity Business Plan Bioscience Judging Committee

2016 Volunteer, American Society for Virology 2016, Conference Volunteer, June 18 - 22, Blacksburg, VA

2016 - 2017 Mentor, The American Gastroenterologist Association International Clinical and Research Education (CORE) Program

2017 United States Invited Representative, 2017 PLoS One International Section Editor Summit, March 24-25, Cambridge, UK.

2017 – 2021 Member, Society for Mucosal Immunology Professional Development and Education Committee

2017 - 2018 Member, Society for Leukocyte Biology Professional Development Committee
2018 Invited Participant in NanoEarth 2018
2019 Member, Mentor Selection Committee, Society for Mucosal Immunology

UNIVERSITY SERVICE:

2007 - 2012 Laboratory Animal Coordinator, IACUC, UNC Office of Animal Care and Use, UNC Chapel Hill
2011 - 2012 Member, Training and Compliance Group, Office of Animal Care and Use, Laboratory Animal Training Consultant and Trainer, UNC Chapel Hill
2013 – 2014 Member, University Veterinarian and Director of the Office of Animal Resources Search Committee, Virginia Tech
2013 – 2015 Member, Undergraduate Honor System Faculty Hearing Board Member, Virginia Tech
2015 - 2016 Search Committee Member, Clinical Laboratory Veterinarian, Office of the University Veterinarian, Virginia Tech
2015 – 2023 Member, Institutional Biosafety Committee (IBC), Virginia Tech
2016 Faculty Design Team, Adaptive Brain and Behavior Destination Area, Virginia Tech
2021 Reviewer, Genetics, Bioinformatics, and Computational Biology University Programmatic Review
2022 – 2025 Alternate Member, Virginia Tech Institutional Animal Care and Use Committee (IACUC)
2023 Search Committee Member, Clinical Laboratory Veterinarian, Office of the University Veterinarian, Virginia Tech

COLLEGE SERVICE:

2014 – 2018 Member, Research Committee, VMCVM
2015 MMI Faculty Interviewer for Class of 2019, VMCVM
2015 Member, John Johnson Award for Graduate Student Excellence in Microbiology Selection Committee, Virginia Tech
2015 Application Reviewer, Interdepartmental Microbiology Graduate Program Admissions Committee, Virginia Tech
2015 - 2024 DVM Honor Code Facilitator, VMCVM
2016 MMI Faculty Interviewer for Class of 2020, VMCVM
2016 - 2021 Member, Summer Veterinary Student Research Program Selection Committee
2017 MMI Faculty Interviewer for Class of 2021, VMCVM
2017 - 2018 Member, Graduate BMVS Curriculum Revision Committee, VMCVM
2018 MMI Faculty Interviewer for Class of 2022, VMCVM
2018 Search Committee Member, VA-MD College of Veterinary Medicine Strategic Content Manager, Stakeholder Group, Virginia Tech
2018 Search Committee Member, Graduate Program Coordinator, Biomedical and Veterinary Sciences (BMVS), VMCVM
2019 MMI Faculty Interviewer for Class of 2023, VMCVM
2019 Reviewer, Phi Zeta Research Competition, VMCVM
2019 Evaluator, M4 Student Research, VTSOM
2020 Member, COVID-19 Response Oversight Team, VMCVM
2021 Member, VMCVM Grants Coordinator Search Committee
2022 Member, Administrative Review Committee, VMCVM
2021 – present Member, BSL3 Management Committee

DEPARTMENT SERVICE:

2013 – 2017	Member, Peer Teaching Evaluation Committee, DBSP
2013 – 2014	Search Committee Member, Cancer Biology Faculty Search Committee, VTCRI
2016 – 2017	Search Committee Member, Department Head Search Committee, Department of Biomedical Sciences and Pathobiology, VMCVM
2016 – present	Member, TBMH Program Admissions Committee
2017	Search Committee Member, Immunology/Infectious Disease Destination Area, VTCRI
2017 – 2019	Search Committee Member, Assistant Professor in Mucosal Immunology, Department of Dairy Science, Virginia Tech
2017 – 2018	Search Committee Member, Virology/Immunology, VTCRI
2019	Member, DBSP Committee for Research Advancement, Virginia Tech
2021 - 2022	Search Committee Member, Brain Cancer, FBRI
2022	Reviewer, Seale Innovation Fund Proposal Review for FBRI
2023 – 2024	Member, Pharm/Tox Search Committee, VMCVM
2023	Member, FBRI Junior Faculty Search Committee, Cancer Research
2023	Member, FBRI Senior Faculty Search Committee, Cancer Research
2023	Reviewer, Seale Innovation Fund Proposal Review for FBRI
2024	Search Committee Member, Avian Health, School of Animal Sciences, VT

INTELLECTUAL PROPERTIES

1. U.S. Patent 11,311,329, "TREATMENT PLANNING FOR IMMUNOTHERAPY BASED TREATMENTS USING NON-THERMAL ABLATION TECHNIQUES", Awarded: April 26, 2022. Filing Date: March 13, 2019; Inventors: Rafael V. Davalos, Natalie Beitel White, Nikolaos Dervisis, **Irving Coy Allen**

2. U.S. Patent Application: ELECTROPORATION-BASED PLATFORM FOR GENERATION OF TUMOR-ACTIVATED T CELLS; Inventors: Rafael V. Davalos, **Irving C. Allen**, Scott S. Verbridge, Nastaran Alinezhadbalalami; VTIP-A1018-PCT; Application No. PCT/US21/51551; File Date: September 22, 2021; Patent Pending

3. U.S. Patent Application: PERSULFIDE DONORS ACTIVATED IN THE GUT; Serial No.: 63/128,491; Filing Date: 12/21/2020; Inventors: John Matson, Kearsley M. Dillon, **Irving C. Allen**; VTIP No.: 21-061 T|H Docket No.: 222204-8135 Disclosure

4. U.S. Patent Application: SYSTEMS AND METHODS OF USING PULSED ELECTRIC FIELDS TO SPATIALLY CONTROL CELL DEATH MECHANISMS THAT MODULATE THE IMMUNE RESPONSE; Serial No.: 63/318,996; 63/323,098; 63/414,773; Application No. PCT/US23/15118. Application Filing Date: 03/13/2023; Inventors: Rafael V. Davalos, Nastaran Alinezhadbalalami, Kenneth Aycock, **Irving Coy Allen**; VTIP No.: 22-013 Disclosure

PUBLICATIONS

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3. Schmidt, S., Postel, E.A., Agarwal, A., **Allen, I.C. Jr.**, Walters, S.N., De La Paz, M.A., Scott, W.K., Haines, J.L., Pericak-Vance. M.A., Gilbert, J.R. (2003). Detailed Analysis of Allelic Variation in the *ABCA4* Gene in Age-Related Maculopathy. *Investigative Opthalmology and Visual Science*. July 44(7):2868-2875. PubMed PMID: 12824224. *IF: 3.73*
4. Raiford, K.L., Shao, Y., **Allen, I.C.**, Martin, E.R., Menold, M.M., Wright, H.H., Abramson, R.K., Worley, G., DeLong, G.R., Vance, J.M., Cuccaro, M.L., Gilbert, J.R., and Pericak-Vance, M.A. (2004). No Association between the *APOE* Gene and Autism. *American Journal of Medical Genetics Part B (Neuropsychiatric Genetics)*. 125B:57-60. PubMed PMID: 14755445. *IF: 3.368*
5. Li, Y., Pericak-Vance, M. A., Haines, J.L., Siddique, N., McKenna-Yasek, Diane, Hung, W., Sapp, P., **Allen, I.C.**, Chen, W., Hosler, B., Saunders, A.M., Dellefave, L.M., Brown, R.H., Siddique, T. (2004). Apolipoprotein E is associated with age at onset of amyotrophic lateral sclerosis. *Neurogenetics*.5:209-213. PMID: 15657798. *IF: 3.37*
6. **Allen, I.C.**, Hartney, J.M., Coffman, T.M., Penn, R.B., Wess, J., Koller, B.H. (2006). Thromboxane A2 Induces Airway Constriction through an M3 Muscarinic Acetylcholine Receptor Dependent Mechanism. *American Journal of Physiology - Lung, Cell and Molecular Physiology*. 290: 526-533. PubMed PMID: 16243899. *IF: 4.19*
7. **Allen, I.C.**, Pace, A.J., Jania, L.A., Ledford, J.G., Latour, A.M., Snouwaert, J.N., Therien, A.G., Bernier, V., Stocco, R., and Koller, B.H. (2006). Expression and function of NPSR1/GPRA in the lung before and after induction of asthma like disease. *American Journal Of Physiology - Lung, Cell and Molecular Physiology*. 291(5): 1005-1017. PubMed PMID: 16829631. *IF: 4.19*
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10. Willingham, S.B.*****, **Allen, I.C.***, Bergstralh, D.T.*****, Brickey, W.T., Taxman, D.J., Duncan,J.A. Ting, J.P.Y. (2009). *Klebsiella pneumoniae* induces IL-1β release and pyronecrosis through NLRP3. *The Journal of Immunology*. August;183(3):2008-2015. PubMed PMID: 19587006; PubMed Central PMCID:PMC3652593. *IF: 5.67.* *Authors Contributed Equally.
11. Craven, R.R., Gao, X., **Allen, I.C.**, Gris, D., Bubeck-Wardenburg, J., Schneewind, O., Ting, J.P., Duncan, J.A. (2009). *Staphylococcus aureus* α hemolysin induces caspase-1 activation and inflammatory cell death through activation of the NLRP3 inflammasome. *PLoS One*. Oct 14;4(10):e7446. PubMed PMID: 19826485; PubMed Central PMCID: PMC2758589. *IF: 4.244*
12. **Allen, I.C.** (2009). Searching for an Improved Mouse Model of Allergic Airway Disease Using Dual Allergen Exposures. *Disease Models and Mechanisms*. Nov-Dec;2(11-12):519-20. PubMed PMID: 19892879. *IF: 5.01*
13. **Allen, I.C.**, Tekippe, E.M., Woodford, R.M., Uronis, J.M., Holl, E.K., Rogers, A.B., Herfarth, H.H., Jobin, C., Ting, J.P.Y. (2010). The NLRP3 Inflammasome Functions as a Negative Regulator of Tumorigenesis during Colitis Associated Cancer. *The Journal of Experimental*

Medicine. May 10;207(5):1045-56. PubMed PMID: 20385749; PubMed Central PMCID: PMC2867287. *IF: 14.10*

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28. Holl,E.K., Roney,K., **Allen,I.C.**, Steinbach,E., Arthur,J., Buntzman,A., Plevy,S., Frelinger, J. Ting,J.P.Y. (2012). Plexin-B2 and Plexin-D1 in Dendritic Cell: Expression and IL-12/IL-23p40 production. *PLoS One*. 7(8):e43333. PubMed PMID: 22916243; PubMed Central PMCID: PMC3419716. *IF: 4.244.*
29. **Allen,I.C.**, McElvania-TeKippe, E., Lich, J.D., Arthur, J.C., Sullivan, J.T., Braunstein, M., Ting, J.P.Y. (2013). Characterization of NLRP12 during the in vivo host immune response to *Klebsiella pneumoniae* and *Mycobacterium tuberculosis*. *PLoS One*. 8(4):e60842. PubMed PMID: 23577168; PubMed Central PMCID: PMC3618512. *IF: 4.244*
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35. Williams, T.M., Leeth,R.A., Rothschild,D.E., McDaniel,D.K., Coutermarsh-Ott,S.L., Simmons,A.E., Kable,K.H., Heid,B., **Allen,I.C.** (2015). Caspase-11 Attenuates Gastrointestinal Inflammation and Experimental Colitis Pathogenesis.*AJP-Gastrointestinal and Liver Physiology*. Jan 15;308(2):G139-50. PMID: 25414099. *IF: 3.853.*

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116. Morrison, H.A., Trusiana, B., Rowe, A.J., **Allen, I.C.** (2023). Negative Regulatory NLRs Mitigate Inflammation via NF-κB Pathway Signaling in Inflammatory Bowel Disease. *Biomedical Journal*. Jun 14;46(5):100616. PMID: 37321320. Invited Review. *IF: 7.892*
117. Imran, K.M., Ganguly, A., Paul, T., Powar, M., Vlaisavljevich, E., Cho, C.S., **Allen, I.C.** (2023). Magic Bubbles: Utilizing Histotripsy to Modulate the Tumor Microenvironment and Improve Systemic Anti-Tumor Immune Responses. *International Journal of Hyperthermia*. 40(1):2244206. PMID: 37580047. Invited Review. *IF: 3.98*
118. Nagai-Singer, M.A., Woolls, M.K., Leedy, K., Hendricks-Wenger, A., Brock, R.M., Coutermarsh-Ott, S., Morrison, H.A., Imran, K.M., Tupik, J.D., Fletcher, E.J., Brown, D.A., **Allen, I.C.** (2023). Cellular context dictates the suppression or augmentation of triple-negative mammary tumor metastasis by NLRX1. *The Journal of Immunology*. Nov1: ji2200834. PMID: 37909827. *IF: 5.422*

119. Salameh, Z.S., Aycock, K.N., Alinezhadbalalami, N., Imran, K.M., McKillop, I.H., **Allen, I.C.** Davalos, R.V. (2023). Harnessing the Electrochemical Effects of Electroporation-Based Therapies to Enhance Anti-Tumor Immune Responses. *Annals of Biomedical Engineering*. Nov 21. doi: 10.1007/s10439-023-03403-x. PMID: 37989902. *IF: 4.219*
120. Hay, A.N., Vickers, E.R., Patwardhan, M., Gannon, J., Ruger, L., **Allen, I.C.**, Vlaisavljevich, E., Tuohy, J. (2023). Investigating cell death responses associated with histotripsy ablation of canine osteosarcoma. *International Journal of Hyperthermia*. 40(1):2279027. *IF: 3.98*.
121. Mott, M., Trusiano, B., **Allen, I.C.** (2024). Buena VISTA: A Promising Outlook on Targeting Immune Checkpoint Regulators to Combat Sepsis. *Journal of Leukocyte Biology*. May 29;115(6):1002-1004. Invited Review. *IF: 6.011.*
122. Trusiano, B., Zimmerman, K.L., Morrison, H.A., **Allen, I.C**. (2024). Not just for lymphoid cells: The role of the noncanonical NF-kB signaling pathway in early and late myelopoiesis with a focus on hypereosinophilic disorders. *The Journal of Leukocyte Biology*. Jul 25;116(2):297-306. Invited Review. *IF: 6.011*.
123. Imran, K.M., Brock, R.M., White, N., Powar, M., Orr, K.N, Aycock, K.N., Alinezhadbalalami, N., Salameh, Z.S., Eversole, P., Tintera, B., Markov-Madanick, J.W., Hendricks-Wenger, A., Coutermarsh-Ott, S., Davalos, R.V., **Allen, I.C.** (2024). Irreversible electroporation promotes a proinflammatory tumor microenvironment and anti-tumor immunity in pancreatic cancer. *Frontiers in Immunology*. Apr 22;15:1352821. *IF: 7.30*.
124. Morrison, H.A., Eden, K., Trusiano, B., Rothschild, D.E., Qin, Y., Wade, P.A., Rowe, A., Mounzer, C., Stephens, M.C., Hanson, K.M., Brown, S.L., Holl, E.K., **Allen, I.C.** (2024). NF-κB Inducing Kinase Attenuates Colorectal Cancer by Regulating Noncanonical NF-κB Mediated Intestinal Epithelial Cell Regeneration. *Cellular and Molecular Gastroenterology and Hepatology*. May 14;18(3):101356. *IF: 7.2.*
125. David, K.M., Alinezhadbalalami, N., Salameh, Z., Aycock, K.N., **Allen, I.C.**, Davalos, R.V. 2024. Modulating the Cell Death Immune Response for Electroporation Treatments. *Bioelectrochemistry*. (In Press 07/09/2024). *IF: 5.76*
126. Porier, D.L., Adam, A., Kang, L., Michalak, P., Tupik, J., Santos, M.A., **Allen, I.C.**, Wang, T., Auguste, A.J. 2024. Humoral and T-cell-mediated responses to a pre-clinical Zika vaccine candidate that utilizes a unique insect-specific flavivirus platform. *PLoS Pathogens*. 2024 Oct 10;20(10):e1012566. doi: 10.1371/journal.ppat.1012566. eCollection 2024 Oct. PMID: 39388457. *IF: 6.70*
127. Khan M., Irvin P., Park S.B., Ivester H.M., Ricardo-Lax I., Leek M., Grieshaber A., Jang E.S., Coutermarsh-Ott S.L., Zhang Q., Maio N., Jiang J.K., Li B., Huang W., Wang A.Q., Xu X., Hu Z., Zheng W., Ye Y., Rouault T., Rice C.M., **Allen I.C.**, Liang T.J. 2024. Repurposing of lonafarnib as a treatment for SARS-CoV-2 infection. JCI Insight. 2024 Dec 3:e182704. doi: 10.1172/jci.insight.182704. Online ahead of print. PMID: 39625789. IF: 6.3

BOOKS:

1. Mouse Models of Innate Immunity. *Methods in Molecular Biology*, Volume 1031
   Irving C. Allen,ed. New York: Humana Press. 2013.
   *16,964 Chapter Downloads in 2013; Top 25% most downloaded Springer eBooks
   Authored Chapters:
   1. **Allen,I.C.** (2013). Bacteria-Mediated Acute Lung Inflammation. *Methods in Molecular Biology*. 1031:163-75. PMID: 23824899.
   2. **Allen,IC.** (2013). Delayed-type Hypersensitivity Models in Mice. *Methods in Molecular Biology*.1031:101-7. PMID: 23824893.

3. Moore, C.B. and **Allen,I.C.** (2013). Primary Ear Fibroblast Derivation from Mice. *Methods in Molecular Biology*. 1031:65-70. PMID: 23824888.

2. Mouse Models of Allergic Disease. *Methods in Molecular Biology*, Volume 1032
Irving C. Allen,ed. New York: Humana Press. 2013.
Authored Chapters:
1. **Allen, I.C.** (2013). Induction of Allergic Airway Disease Using House Dust Mite Allergen. *Methods in Molecular Biology*.1032:159-72. PMID: 23943452.
2. **Allen, I.C.** (2013). Contact Hypersensitivity Models in Mice. *Methods in Molecular Biology*. 1032:139-44. PMID: 23943450.

3. Mouse Models of Innate Immunity, 2nd Edition. *Methods in Molecular Biology*, Volume 1960. **Irving C. Allen, ed.** New York: Humana Press. 2019. Invited Book.
*31,533 Chapter Downloads in 2019; Top 25% most downloaded Springer eBooks
Authored Chapters:
1. Ringel-Scaia, V.M., Powell, M.D., Read, K.A., **Allen, I.C.**, Oestreich, K. (2019). Systemic *Listeria monocytogenes* infection as a model to study T helper cell immune responses. *Methods in Molecular Biology.* 2019;1960:149-160. PMID: 30798529.
2. McDaniel, D.K. and **Allen, I.C.** (2019). Using *Klebsiella pneumoniae* to Model Acute Lung Inflammation in Mice. *Methods in Molecular Biology.* 2019;1960:169-180. PMID: 30798531.

INVITED BOOK CHAPTERS:

1. Tilley, S.L., **Allen, I.C.**, Koller, B.H. (2006). Generation of Genetically Manipulated Mouse Lines for the Study of Asthma. In: Genetics of Asthma and COPD, edited by Dirkje Postma and Scott Weiss. New York:Taylor & Francis Group, LLC, p.127-158.
2. Ringel, V., **Allen, I.C.** (2016). The Application of Nanotechnology to Gastrointestinal Cancers. In Gastrointestinal Cancers: Prevention, Detection and Treatment, Volume 2. Edited by Amit Tyagi and Sahdeo Prasad. New York: NOVA Science Publishers, p.271-290.
3. McDaniel, D.K., Ringel-Scaia, V.M., Coutermarsh-Ott, S.L., **Allen, I.C.** (2018). Utilizing the Lung as a Model to Study Nanoparticle Based Drug Delivery Systems. *Targeted Drug Delivery: Methods and Protocols.* Part of the *Methods in Molecular Biology* Series. Rachael Sirianni and Bahareh Behkam, eds. New York: Humana Press. 1831:179-190. PMID: 30051432.
4. Hendricks-Wenger, A., Nagai-Singer, M.A., Uh, K., Vlaisavljevich, E., Lee, K., **Allen,I.C.** (2022). Employing Novel Porcine Models of Subcutaneous Pancreatic Cancer to Evaluate Tumor Ablation Strategies. Biosensors and Biodetection, 3rd edition. In *Methods in Molecular Biology*. Ed. Avraham Rasooly and Ben Prickril. Humana Press. 2394:883-895. PMID: 35094364. Invited Book Chapter.
5. Ivester, H.M., Tupik, J.D. Nagai-Singer, M.A., Coutermarsh-Ott, S.L., **Allen, I.C.** (2022). Methods to Evaluate Virus-Mediated Acute Lung Inflammation. 2022. *Methods in Cell Biology: Inflammation, Infection, and Injury*. Edited by David C. Montrose. Elsevier. 168:329-341. PMID: 35366990. Invited Book Chapter.

THESIS AND DISSERTATION:

1. **Allen, Irving C. Jr.** Utilization of the Polymerase Chain Reaction and Fluorescent *In Situ* Hybridization to Assess Fine Scale and Global Distribution Patterns of *Pfiesteria* species. MS Thesis, Department of Biology. The University of North Carolina at Greensboro. Greensboro, NC, 2000. 101 pp.
2. **Allen, Irving C. Jr.** G Protein-Coupled Receptors in the Neuropathophysiology of Asthma. Ph.D Dissertation, The Curriculum of Genetics and Molecular Biology. The University of North Carolina at Chapel Hill. Chapel Hill, NC, 2006. 232 pp.

SEMINARS, PRESENTATIONS, AND ABSTRACTS

INVITED SEMINARS (last 2 years; selected out of 47 total)

1. "Histotripsy and Immune Effects". Invited Speaker. 2023 Society of Interventional Radiology Annual Meeting. Phoenix, AZ. March 4-9, 2023.
2. "Financial Skills for Lab Management". Invited Speaker. 2023 Society for Leukocyte Biology Webinar Series. June 21, 2023.
3. Invited Attendee of the 2023 Meeting of the Society for Leukocyte Biology. Athens, Georgia September 27-30, 2023.
4. Invited Attendee to the 12th Biennial Symposium of the International Eosinophil Society. Hamilton, Canada. July 13-16, 2023.
5. "Emerging IO therapies from an immunology perspective". Invited Speaker. 2024 Society of Interventional Radiology Annual Meeting. Salt Lake City, Utah. March 23-28.
6. "Immunology 101". Invited Speaker. Intuitive Surgical Virtual Address. July 23, 2024.
7. "The Importance of Undergraduate Research". Invited Keynote Address. 2024 Undergraduate Research Symposium. Virginia Tech. Blacksburg, VA. July 25, 2024.
8. "A NOD" To Maintaining Immune System Homeostasis During Host-Virus Interactions". Invited Speaker. West Virginia University. Morgantown, WV. October 3rd, 2024. Host: Dr. Salik Hussain
9. Invited Attendee of the 2024 Meeting of the Society for Leukocyte Biology. East Lansing, MI. October 22-24, 2024.
10. "Magic Bubbles: Turning Immunologically "Cold" Tumors "Hot" and Augmenting Systemic Anti-Tumor Immunity Using Histotripsy". Invited Speaker. Wake Forest Comprehensive Cancer Center. Winston Salem, NC. October 25, 2024. Hosts: David Soto-Pantoja and David Foureau.
11. "Immunological Effects of Focused Ultrasound in Pancreatic Cancer Preclinical Models". Invited Speaker. The Role of Focused Ultrasound in Pancreatic Cancer Workshop at The University of Virginia. Charlottesville, VA. November 7-8, 2024. Host: The Focused Ultrasound Foundation.

Invited Chair or Moderator:

1. "Emerging Concepts in NLR Sensing and Signaling". Organizer and Co-Chair, Society for Leukocyte Biology Annual Meeting, Satellite Symposium, October 13-17, 2019. Chandler, AZ
2. Crohn's and Colitis Foundation Investigators Research Symposium. Invited Moderator. October 12th-13th, 2021. Virtual Session.
3. Resident Microbes that Induce Aggressive vs Protective Responses in Genetically Predisposed vs Normal Hosts. Invited Moderator. Society for Leukocyte Biology 2020 Virtual Session (Portland, OR). June 4, 2020.
4. "Beyond Academia: Career Paths and Options". Workshop Organizer. Society for Leukocyte Biology 2020 Annual Meeting. Virtual Workshop (Portland, OR). October 3, 2020.
5. "Novel RNAi Inhibition of Inflammation Signaling". Invited Moderator. Society for Leukocyte Biology 2021 Virtual Session. May, 2021.
6. "Pathogen Control and Evasion". Chair. Block Symposium at Virtual Immunology 2021. Annual Meeting of the American Association of Immunologist. May, 2021.
7. "The Art of Productive Research Mentoring: Best Practices for Meaningful Mentor/Mentee Relationships". Workshop Organizer. Society for Leukocyte Biology 2021 Annual Meeting. Virtual Workshop. June 28th, 2021.
8. "The Impact of the Commensal Microbiome on Cancer Progression and Therapy Response". Invited Chair. Block Symposium at Immunology 2022. Annual Meeting of the American Association of Immunologist. Portland, OR. May 6-10, 2022.
9. "Tumor Immunology". Invited Chair. Plenary Session at the Southeastern Immunology Symposium. Durham, NC. June 11-13, 2022.

10. "Histotripsy Cancer Treatment: The Road from Bench to Bedside". Dr. Zhen Xu. Invited Moderator. International Symposium on Therapeutic Ultrasound. Webinar. March 16, 2023.

Scientific Presentations at Professional Meetings (selected out of 145):

1. "NLRX1 attenuates inflammation and tumorigenesis through the negative regulation of AKT and NF-κB signaling". S Coutermarsh-Ott; A Simmons; V Capria; T LeRoith; C Washington; N Dervisis; V Yuzbasiyan-Gurkan; R Hontecillas-Magarzo; J Bassaganya-Riera; J Ting, **Allen, I.C.** Oral and Poster Presentation, International Conference: Keystone Conference Z4: Mechanisms of Pro-inflammatory Diseases, Olympic Valley, CA. April 19-24, 2015.
2. "Caspase-11 modulates inflammation and attenuates Toxoplasma gondii pathogenesis". **Allen, I.C.**** Oral and Poster Presentation at the International Congress of Immunology (ICI) 2016 annual meeting. August 21-26, 2016. Melbourne, Australia.
3. "IRAK-M Splice Variant Attenuates Inflammatory Bowel Disease and Colitis Associated Tumorigenesis". **Allen, I.C.****. Oral, Poster, and ePoster Presentation at the International Meeting of the Society for Mucosal Immunology, Mucosal Immunology Course and Symposium, Microbiota and Mucosal Immunity: Rules of Engagement in Health and Disease. June 27-30, 2016. Toronto, Canada.
4. "Ablation of NF-κB Inducing Kinase (NIK) Results in Eosinophilic Esophagitis (EoE) and Gastric Hyperplasia". **Allen, I.C.**.** Oral and Poster presentation at the 18th International Congress of Mucosal Immunology (ICMI 2017), July 19-22, 2017. Washington, DC.
5. "Map3K14 signaling attenuates the development of colorectal cancer through activation of the non-canonical NF-kB signaling cascade". **Allen, I.C.**.** Oral and Poster presentation at Immunology 2017, the annual meeting of the American Association of Immunologist, May 12-18, 2017. Washington, DC.
6. "Novel NOD-like receptor family members regulate neuroinflammation and maintain immune system homeostasis following traumatic brain injury". **Allen, I.C.****. Oral Presentation. 2018 National Capital Area TBI Research Symposium, March 6-7, 2018. NIH, Bethesda, MD.
7. "Utilization of high-frequency irreversible electroporation (H-FIRE) to modulate the tumor microenvironment and promote systemic immune system activation in breast cancer." V. M. Ringel-Scaia, R. M. Brock, S. L. Coutermarsh-Ott, K. E. Huie, N. Beitel White, M. F. Lorenzo, R. V. Davalos, **I. C. Allen**. 5th European Congress of Immunology. September 2-5, 2018. Amsterdam, NL.
8. "Irreversible Electroporation is an Effective Tumor Ablation Strategy that Induces Immunologic Cell Death and Promotes Systemic Anti-Tumor Immunity". **Allen, I.C.** Oral Presentation and Poster Presentation. AACR Tumor Immunology and Immunotherapy Conference. November 17 - 21, 2019. Boston, MA.
9. Keystone Symposia on Molecular and Cellular Biology, COVID-19: One Year Later (EK32), Participant; February 8-9, 2021

MEDIA COVERAGE:

1. February 05, 2015 "Cancer and the Immune System", Interviewed by Jim Metzner on *National Public Radio*, Pulse of the Planet
2. February 09, 2015 "Cancer the Chess Master", Interviewed by Jim Metzner on *National Public Radio*, Pulse of the Planet
3. February 10, 2015 "Cancer – Mutations", Interviewed by Jim Metzner on *National Public Radio*, Pulse of the Planet
4. March 1, 2017 "Researchers pair with artists to make science more accessible", *Roanoke Times*. Interviewed by Robby Korth.

5. ‘COVID-19 Immunity Could Be Long Term.’ Popular Science. Interviewed by Kate Baggaley. Published 1/8/2021. https://www.popsci.com/story/health/covid-19-immune-response-antibodies-long-term/
6. ‘Deaths After Pfizer COVID Vaccines Not Linked to Shots, Says European Medicines Agency.’ Newsweek. Interviewed by Aristos Georgiou. Published 1/29/2021. https://www.newsweek.com/pfizer-biontech-covid-vaccine-deaths-eu-medicines-agency-1565405
7. 'Knowing how long immunity lasts is a key battleground in the fight against COVID.' Mirror. Interviewed by Miriam Stoppard. Published 2/7/ 2021. https://www.mirror.co.uk/lifestyle/health/why-knowing-how-long-immunity-23458219
8. ‘Ultrasound Cavitation Improves Delivery of Pancreatic Cancer Therapies.’ Focused Ultrasound Foundation. Interviewed by Jill Roberts. Published 7/6/2023. https://www.fusfoundation.org/posts/ultrasound-cavitation-improves-delivery-of-pancreatic-cancer-therapies/

RESEARCH SUPPORT:

EXTRAMURAL

1. NLR Regulation of Innate Immune Responses to Respiratory Virus Infection
F32 NIH - NIAID (**PI: Allen**) 09/01/09 – 12/31/10

2. NLR Regulation of Gastrointestinal Inflammation and Tumorigenesis
PF-10-053-01-LIB The American Cancer Society (**PI: Allen**) 01/01/10 – 06/30/11

3. NLR Regulation of Gastrointestinal Inflammation and Tumorigenesis
P30 UNCCH/CGIBD (**PI: Allen**) 07/01/09 – 02/29/11

4. NLR Regulation of Gastrointestinal Inflammation and Tumorigenesis
K01 NIH – NIDDK (**PI: Allen**) 07/01/11 – 06/30/16

5. Evaluating NLR Modulation of Canonical and Non-Canonical NF-kB Signaling in IBD
R03 NIH – NIDDK (**PI: Allen**) 07/01/15 – 06/30/17

6. Immunosignature Differentiation of Lymphoma and Inflammatory Bowel Disease in Cats
Winn Foundation (**Co-I: Allen**) 01/01/16 – 12/31/16

7. The Contribution of NLR Proteins in Modulating Gastrointestinal Inflammation Following Exposure to Wheat Gluten
One Health Center Seed Fund VCOM (**PI: Allen**) 11/10/15 – 06/30/17

8. Using an Approved Device to Increase the Immune Response in Pancreatic Cancer Patients
Research in Progress Cures Within Reach (**Co-I: Allen**) 11/01/16 – 10/31/17

9. Role of the Non-Canonical NF-kB Inflammatory Cascade in Therapeutic Response and Pathogenesis of Inflammatory Bowel Disease
RAP Tier I Carilion Clinic (**PI: Allen**) 07/01/17 – 12/31/18

10. Evaluation of pro-inflammatory TH2 mediated biomarkers and NF-kB signaling pathways in the Diagnosis and Treatment of Eosinophilic Esophagitis (EoE)
RAP Tier II Carilion Clinic (**Co-I: Allen**) 07/01/17-12/31/18

11. Defining the roles of inflammasomes in Zika virus infection
4-VA (**PI: Allen**) 05/01/17 – 04/30/18

12. NLR Modulation of the Gut Microbiome during Celiac Disease

One Health Center Seed Fund VCOM (**PI: Allen**) 07/01/17 – 06/30/18

13. Regulation of T helper cell differentiation by integrated STAT and Ikaros zinc finger transcription factor mechanisms
R56 NIH/NIAID (**Co-I: Allen**) 08/01/17 - 07/31/18

14. Investigation of the immunostiumulatory response to high frequency ultrasound in dogs with naturally occurring solid tumors
Focused Ultrasound Foundation (**Co-I: Allen**) 01/01/18 – 12/31/18

15. Effect of Magnéli phase titanium oxide nanoparticles in the mammalian respiratory tract
Center for Environmental Implications of Nanotechnology Duke University 09/01/17 – 12/31/17
(**PI: Allen)**

16. Careers in Immunology Fellowship
American Association of Immunologist (**PI: Allen**) 09/01/17 – 08/31/18

17. Mechanistic role of probiotic Lactobacillus reuteri in autoimmune lupus
R01 NIH - NIAMS (**Co-I: Allen**) 07/01/18 – 06/30/23

18. Identifying novel regulatory pathways underlying T helper 1 cell immune responses
R01 NIH - NIAID (**Co-I: Allen**) 07/01/18 – 06/30/23

19. Top-Down or Bottom-Up Tumorigenesis: Defining the role of non-canonical NF-κB signaling in colorectal cancer
One Health Center Seed Fund VCOM (**PI: Allen**) 07/01/18 – 06/30/19

20. Elucidating Mechanisms Modulated by NIK and Non-Canonical NF-κB Signaling In Colorectal Cancer
One Health Center Seed Fund VCOM (**PI: Allen**) 07/01/19 – 06/30/20

21. Development of Novel Porcine Models of Orthotopic Pancreatic Cancer for FUS and Histotripsy Tumor Ablation Applications
Focused Ultrasound Foundation (**PI: Allen**) 07/01/19 – 06/30/20

22. Employing Novel Porcine Models of Orthotopic Pancreatic Cancer to Evaluate Histotripsy Based Tumor Ablation Strategies
R21 NIH - NIBIB (**PI: Allen)** 07/01/19 – 06/30/21

23. Effects of probiotic strains on intestinal immunity of germ-free mouse
Zhejiang University VT Foundation (**Co-I: Allen**) 06/01/19 – 05/31/20

24. A Tissue Engineering Approach to Analyzing Host-Microbe Interactions in Cancer
R21 NIH - NCI (**Co-I: Allen**) 08/01/19 – 07/31/21

25. Non-invasive Focused Ultrasound Ablation for the Treatment of Cholangio-carcinoma Liver Tumors
Focused Ultrasound Foundation (**Co-I: Allen**) 07/01/19 – 06/30/20

26. Targeting the peptidoglycan cell wall of *Borrelia burgdorferi* to diagnose and treat Lyme disease
Steven and Alexandra Cohen Foundation (**Co-I: Allen**) 01/01/20 – 12/31/22

27. Defining Mechanisms Regulated by Nonocanonical NF-κB Signaling that Modulate Eosinophilic Esophagitis
iTHRIVE Pilot Translational and Clinical Studies Program (**PI: Allen**) 02/01/20 – 01/31/21

28. Nanoparticle-mediated Histotripsy (NMH) for Noninvasive and Targeted Ablation of Metastatic Breast Cancer
R21 NIH - NIBIB Trailblazer (**Co-I: Allen**) 01/20/20 - 12/31/22

29. Histotripsy for treatment of canine appendicular osteosarcoma
AKC Canine Health Foundation Oak Grant (**Co-I: Allen**) 02/01/20 – 01/31/21

30. Development of an improved vaccine against Brucella abortus
R03 NIH - NIAID (**Co-I: Allen**) 03/01/20 - 02/28/22

31. A novel strategy for generating safe and effective Flavivirus vaccines
R01 NIH -NIAID (**Co-I: Allen**) 06/01/20 - 05/31/25

32. Utilizing Novel Model Systems to Define Novel Mechanisms Controlled by the Unique Kinase NIK during Colorectal Cancer
One Health Center Seed Fund VCOM (**PI: Allen**) 07/01/20 – 06/30/21

33. Characterizing the analgesic, ablative, and oncologic outcomes after histotripsy ablation of osteosarcoma in an orthotopic murine model
One Health Center Seed Fund VCOM (**Co-I: Allen**) 07/01/20 – 06/30/21

34. Investigation of the immunostimulatory response to mechanical high intensity focused ultrasound (histotripsy) in dogs with naturally-occurring soft tissue tumors
Focused Ultrasound Foundation (**Co-I: Allen**) 03/01/20 – 02/28/21

35. Histotripsy as a novel limb salvage treatment and immunotherapy for osteosarcoma
R21 NIH - NIBIB (**Co-I: Allen**) 11/01/20 – 10/31/23

36. Detecting released peptidoglycan fragments as a biomarker for direct diagnosis of acute and chronic Lyme disease
R21 NIH - NIAID (**Co-I: Allen**) 03/01/21 – 02/28/23

37. Deciphering Complex Regulatory Mechanisms Targeting Noncanonical NF-κB Signaling During Colorectal Cancer
One Health Center Seed Fund VCOM (**PI: Allen**) 07/01/21 – 06/30/22

38. Developing Methods for Precise, Safe and Target-location Specific Histotripsy of Liver Tumors
R01 Sub-Contract University of Wisconsin Madison (**PI: Allen**) 07/01/21 – 06/30/26

39. Breaking down the wall: Targeting peptidoglycan to understand and diagnose Lyme Disease
Global Lyme Alliance (**Co-I: Allen**) 11/03/21 – 11/02/23

40. Deploying Histotripsy Based Tumor Ablation Strategies to Treat Pancreatic Cancer
R01 NIH -NCI (**PI: Allen**) 04/15/22 – 04/14/27

41. Investigating the immunomodulation effects of histotripsy ablation in osteosarcoma
Focused Ultrasound Foundation (**Co-I: Allen**) 07/01/22 – 06/30/24

42. Ultrasound-guided Intrinsic Threshold Histotripsy for the Non-invasive Ablation of Uterine Fibroids
R21 NIH - NICHD (**Co-I: Allen**) 08/15/22 – 07/31/24

43. Optimization of High Frequency Irreversible Electroporation (H-FIRE) for tumor ablation and immune system activation in pancreatic cancer applications

R01 NIH - NCI (**PI: Allen)** 04/01/23 – 03/31/28

44. Advancing histotripsy towards clinical translation for focused ultrasound ablation of osteosarcoma
Focused Ultrasound Innovation Fund FUSF/FBRI (**Co-I: Allen**) 08/19/23 – 05/31/24

45. Turning Up the Heat: Using Focused Ultrasound to Shift the Immunosuppressive Breast Cancer Tumor Microenvironment from "Cold" to "Hot", Augmenting Systemic Anti-Tumor Immune Activation
Focused Ultrasound Innovation Fund FUSF/FBRI (**PI: Allen**) 08/19/23 – 05/31/24

46. Debulking the Tongue-Base: Image-Guided Histotripsy for Sleep Apnea
Focused Ultrasound Foundation (**Co-I: Allen**) 11/01/23 – 10/31/24

47. Ultrasound-guided Histotripsy for the Complete and Rapid Ablation of Uterine Fibroids
Focused Ultrasound Foundation (**Co-I: Allen**) 01/01/24 – 12/31/24

48. Characterization of a Transesophageal Focused Ultrasound Transducer for Endoscopic Pancreatic Cancer Ablation
Focused Ultrasound Foundation (**Co-I: Allen**) 01/01/24 – 12/31/24

49. Natural History Studies of FSHD Mice and Minipigs
SOLVE FSHD (**Co-I: Allen**) 10/01/24 – 10/01/25

INTRAMURAL

1. Elucidating the Contribution of Negative Regulators of TLR Signaling in Inflammatory Bowel Disease and Tumorigenesis
IRC Pilot Grant VMCVM (**PI: Allen**) 07/01/13 - 06/30/14

2. Development of Novel Genetically Modified Mice to Evaluate Non-Canonical NF-κB Signaling in Inflammatory Bowel Disease
IRC Pilot Grant VMCVM (**PI: Allen**) 07/01/14 - 06/30/15

3. Intrinsic and Extrinsic Determinants of CD4+ TCM Cell Fate
IRC Pilot Grant VMCVM (**PI: Allen**) 03/01/15 – 06/30/16

4. Novel vaccine system against viral infections
Collaboration Seed Grant VMCVM/UMD (**PI: Allen**) 07/01/15 – 06/30/16

5. Harnessing CRISPR Technology for Gene Therapy Applications
JFC Seed Proposal VT-ICTAS (**PI: Allen**) 07/01/15 – 06/30/17

6. Elucidating the Contribution and Therapeutic Potential of NLRX1 Signaling in Histiocytic Sarcoma
IRC Pilot Grant VMCVM (**PI: Allen**) 07/01/15 – 06/30/16

7. Identification of the Transcriptional Network Governing T Follicular Helper Cell Development
IRC Pilot Grant VMCVM (**Co-I: Allen**) 07/01/15 – 06/30/16

8. Sustained Delivery of a Live *Francisella tularensis* Vaccine Strain by Encapsulation
IRC Pilot Grant VMCVM (**Co-I: Allen**) 07/01/15 – 06/30/16

9. Bacteria-based Autonomous Drug Delivery Agents for Cancer Therapy
Translational Nanomedicine Grant VT-ICTAS (**Co-I: Allen**) 07/01/15 – 06/30/16

10. Inhibition of the PI3K Pathway for treating Cancer using Nanoparticle-Based Drug Delivery
Enhanced Drug Delivery Seed Grant VT-ICTAS **(PI: Allen)** 02/01/16 – 01/31/17

11. Evaluating Novel Inflammatory Signaling Pathways from Patients with Inflammatory Bowel Disease
IRC Pilot Grant VMCVM (**PI: Allen**) 07/01/16 – 06/30/17

12. Defining the Roles of Ikaros Zinc Finger (IkZF) Transcription Factors in Central Memory (Tcm) and T Follicular Helper (Tfh) Cell Development
IRC Pilot Grant VMCVM (**Co-I: Allen**) 07/01/16 – 06/30/17

13. Anti-Tumor Microenvironment Modulation Using High Frequency Irreversible Electroporation (H-FIRE)
Seed Funding VT-ICTAS Center for Engineered Health (**PI: Allen)** 01/01/17 – 06/30/17

14. Irreversible electroporation for liver cancer immunotherapy – A pilot study
Veterinary Memorial Fund VMCVM (**Co-I: Allen**) 09/01/17 – 06/30/18

15. Maternal microbiota educates neonatal IgA response
IRC Pilot Grant VMCVM (**Co-I: Allen**) 07/01/17 – 06/30/18

16. Objective method of positive end-expiratory pressure (PEEP) choice to be used in protective ventilation strategies during anesthesia in dogs.
IRC Pilot Grant VMCVM (**Co-I: Allen**) 07/01/17 – 06/30/18

17. Defining Roles for Noncanonical NF-kB Signaling in Eosinophilic Esophagitis
IRC Pilot Grant VMCVM (**PI: Allen**) 07/01/17 – 06/30/18

18. Defining the role of a novel Aiolos/STAT3 transcriptional complex in T_{FH} cell differentiation
IRC Pilot Grant VMCVM (**Co-I: Allen**) 07/01/17 – 06/30/18

19. Mechanisms of Innate Immune Responses to Mindfulness Meditation
Dean's Discovery Fund VT - COS (**PI: Allen**) 07/01/17 – 06/30/18

20. Generating Patient Derived Xenograft Mouse Models of Pancreatic Cancer to Study the Tumor Microenvironment and Anti-Tumor Immunity following IRE Treatment
Seed Funding VT-ICTAS Center for Engineered Health (**PI: Allen)** 01/01/18 – 06/30/18

21. Inhibition of the PI3K Pathway for treating Cancer using Nanoparticle-Based Drug Delivery
Seed Funding VT-ICTAS Center for Engineered Health (**PI: Allen)** 01/01/18 – 06/30/18

22. Novel mechanisms of immune system modulation following hepatitis E virus infection
Collaboration Seed Grant VMCVM/UMD (**PI: Allen**) 01/01/18 – 06/30/18

23. Improving Immune System Engagement in Pancreatic Cancer Using Histotripsy
IRC Pilot Grant VMCVM (**PI: Allen**) 07/01/18 – 06/30/19

24. Novel roles for a lymphocyte-associated transcriptional complex in promoting breast cancer metastasis
IRC Pilot Grant VMCVM (**Co-I: Allen**) 07/01/18 – 06/30/19

25. Persulfide Prodrugs in the Gut: A Microbiome Study
Enhanced Drug Delivery Seed Grant VT-ICTAS (**Co-I: Allen**) 01/01/19 – 06/30/19

26. Pattern Recognition Receptor Driven Suppression of Host-Antiviral Immune Signaling in Hepatitis E Virus Infection
Collaboration Seed Grant VMCVM/UMD (**PI: Allen**) 01/01/19 – 06/30/19

27. Nanoparticle-mediated Histotripsy for the Non-Invasive Treatment of Brain Cancer and other Neurological Disorders
Junior Faculty Award VT-ICTAS (**Co-I: Allen**) 07/01/19 – 06/30/21

28. Characterization of the immunologic responses to HFIRE treatment in the brain
IRC Pilot Grant VMCVM (**Co-I: Allen**) 07/01/19 – 06/30/20

29. Elucidating the microbiome contribution to hypereosinophilic syndromes in the absence of noncanonical NF-κB signaling
IRC Pilot Grant VMCVM (**PI: Allen**) 07/01/19 – 06/30/20

30. Defining Novel Pattern Recognition Receptor Functions During Hepatitis E Virus Infection
Collaboration Seed Grant VMCVM/UMD (**PI: Allen**) 02/05/19 – 05/30/20

31. Establishment of ACE2 transgenic mice colony for COVID-19 research at Virginia Tech
Fralin Life Sciences Institute VT (**PI: Allen**) 04/09/20 – 06/30/20

32. Defining the role of novel pattern recognition receptors in SARS-CoV-2 host immune responses
IRC Pilot Grant VMCVM (**PI: Allen**) 10/10/20 – 06/30/21

33. Targeting bacterial pathogens with prodrugs: Nitroreductase-triggered delivery of persulfides
Seed Funding VT-ICTAS Center for Engineered Health (**PI: Allen**) 10/01/20 – 06/30/21

34. Evaluating the safety and efficacy of a novel vaccine strategy for Cache Valley virus
CeZAP Pilot Grant VT (**Co-I: Allen**) 10/31/20 – 7/31/20

35. Reprogramming the peptidoglycan cell-wall of Borrelia burgdorferi to understand, treat, and cure chronic Lyme disease
CeZAP Pilot Grant VT (**Co-I: Allen**) 10/31/20 – 7/31/20

36. Targeting Unique NOD-like Receptors to Combat the COVID-19 Cytokine Storm
Enhanced Drug Delivery Seed Grant VT-ICTAS (**PI: Allen**) 01/15/21 – 06/30/21

37. Quelling the Storm: Attenuating Overzealous Inflammation Following SARS-CoV-2 Infection by Modulating Regulatory NOD-like Receptor Signaling
CeZAP Pilot Grant VT (**PI: Allen**) 10/07/21 – 6/30/22

38. Defining Cell Type Specific Contributions of NLRX1 in Modulating Host-Pathogen Interactions During SARS-CoV-2 Infection *In Vivo*
IRC Pilot Grant VMCVM (**PI: Allen**) 7/01/21 – 06/30/22

39. Physiological and Electrochemical Effects of Irreversible Electroporation (IRE)
Seed Funding VT-ICTAS Center for Engineered Health (**PI: Allen)** 10/29/21 – 6/30/22

40. Antivirulence-new approach to old foes: Discovery and development of anti-T4P compounds against antibiotic resistant bacteria
CeZAP Interdisciplinary Team-Building Pilot Grant Program (**Co-I: Allen**) 09/21/22 – 06/30/23

41. Quantifying the Role of Fusobacterium nucleatum in Pancreatic Cancer Metastasis
EFO Opportunity Seed Investment Grant VT-ICTAS (**PI: Allen**) 10/17/22 – 6/30/23

42. High-frequency irreversible electroporation as a novel ablation technique for primary lung cancer
Seed Funding VT-ICTAS Center for Engineered (**Co-I: Allen**) 11/01/22 - 06/31/23

43. A pilot study utilizing patient-derived organoids to develop high-frequency irreversible electroporation for osteosarcoma
Veterinary Memorial Fund VMCVM (**Co-I: Allen**) 07/01/23 – 06/31/24

44. Miniaturized high-frequency endoscopic histotripsy transducer for the minimally-invasive treatment of Brain Cancer and other neurological disorders
Center for Engineered Health (**Co-I: Allen**) 07/01/24 – 06/31/24

INDUSTRY SUPPORT:

1. Lactoferrin as a biomarker for the diagnosis and monitoring of inflammatory bowel disease and intestinal lymphoma in dogs
TechLab Inc (**Co-I: Allen**) 01/01/16 – 12/31/16

2. Cellular Response to Low Energy Ele
Boston Scientific **(PI: Allen)** 03/01/17 – 07/31/17

3. Characterization of Irreversible Electroporation in Pancreas
AngioDynamics (**PI: Allen**) 04/01/18 – 04/30/19

4. Characterization of Irreversible Electroporation in Pancreas - Ext
AngioDynamics (**PI: Allen**) 09/12/18 – 04/30/19

5. Defining the Electrical Properties and Biological Impact of Tumor Ablation Modalities for Use In the Prostate to Maximize Therapeutic Impact
AngioDynamics (**PI: Allen**) 09/01/19 – 03/31/21

6. Evaluating Focused Ultrasound Drug Delivery Strategies
OxSonics **(PI: Allen)** 02/01/21 – 02/01/22

7. Evaluating the Safety and Efficacy of Histotripsy in the Pancreas
Histosonics **(PI: Allen)** 08/15/21 – 07/30/26

8. Evaluate the Biodistribution and Delivery of Bioactive Agents Utilizing Nulixir Products
Nulixr (**PI: Allen**) 03/07/24 – 03/06/25

PROGRAM SUPPORT:

1. The Virginia Tech Immunology Summer Journal Club
The Society of Leukocyte Biology (**PI: Allen**) 06/01/15 – 12/31/17

2. NIH K and New Investigator R01 Proposal Preparation Program
Virginia Tech Office of the Vice President for Research and Instruction
Program Development Funds (**PI: Allen**) 01/01/16 – 05/15/17

VIRGINIA TECH DIDACTIC INSTRUCTION:

COURSE AND BLOCK LEADER

2013-present Course Leader, Undergraduate Research (BMVS 4994) for undergraduate students at Virginia Tech, Blacksburg, VA.

2014-2024 Course Developer and Leader, Frontiers of Immunology in Health and Disease (BMVS 6714) for graduate students at Virginia Tech, Blacksburg, VA.

2015-present Course Developer and Leader, Fundamentals of Immunity and Infectious Diseases (TBMH 5054) for graduate students at Virginia Tech, Blacksburg, VA.

2018-2023 Course Developer and Leader, Current Technologies in Biomedical Sciences (BMVS 5594) for graduate students at Virginia Tech, Blacksburg, VA.

2018-present Block Leader, Immunology and Infectious Disease Gateway (TBMH 5004) for graduate students at Virginia Tech, Blacksburg, VA.

2018-2021 Course Leader, BMVS Seminar (BMVS 5944) for graduate students at Virginia Tech, Blacksburg, VA.

INVITED GUEST LECTURES:

2013 Guest lecture, "Inflammation and Mucosal Immunology" for graduate and undergraduate students in the Immunology and Advanced Inflammation Biology (BIOL 4734/5734) course at Virginia Tech, Blacksburg, VA.

2013 Guest lecture, "NLR Inflammasomes" for graduate and students in the Advanced Topics in Immunology (BIOL 6704) course at Virginia Tech, Blacksburg, VA.

2013 Guest lecture, "Mucosal Immunology" for graduate and students in the Advanced Topics in Immunology (BIOL 6704) course at Virginia Tech, Blacksburg, VA.

2013 Guest lecture, "Tumor Immunology" for graduate and students in the Advanced Topics in Immunology (BIOL 6704) at Virginia Tech, Blacksburg, VA.

2014 Guest lecture, "Hypersensitivity" for graduate and undergraduate students in the Immunology and Advanced Inflammation Biology (BIOL 4734/5734) course at Virginia Tech, Blacksburg, VA.

2014 Guest lecture, "Allergy" for graduate and undergraduate students in the Immunology and Advanced Inflammation Biology (BIOL 4734/5734) course at Virginia Tech, Blacksburg, VA.

2014 Guest lecture, "Tumor Immunity" for graduate and undergraduate students in the Immunology and Advanced Inflammation Biology (BIOL 4734/5734) course at Virginia Tech, Blacksburg, VA.

2015 Guest lecture, "Tumor Microenvironment" for graduate students in the Fundamentals of Cancer (TBMH 5024) course at Virginia Tech, Blacksburg, VA.

2015 Guest lecture, "Macrophage Polarization" for graduate students in the Fundamentals of Cancer (TBMH 5024) course at Virginia Tech, Blacksburg, VA.

2015 Guest lecture, "Tumor Immunity" for graduate and undergraduate students in the Immunology and Advanced Inflammation Biology (BIOL 4734/5734) course at Virginia Tech, Blacksburg, VA.

2015 Guest lecture, "Clinical Cancer Research" for graduate students in the Scientific Logic and Analysis (TBMH 5404) course at Virginia Tech, Blacksburg, VA.

2016 Guest lecture, "The Good, The Bad, and the Ugly: Balancing Our Resident Microbes to Promote Health and Wellness" for continuing education students in the Life Long Learning Institute (LLI) sponsored through Virginia Tech, Blacksburg, VA.

2016 Guest lecture, "Intestinal Mucosal Immune System" for graduate students in the Fundamentals of Cancer (TBMH 5024) course at Virginia Tech, Blacksburg, VA.

2016 Guest lecture, "Immune Cells and Crosstalk: Introduction to Immunology" for graduate students in the Translational Biology, Medicine, and Health (TBMH 5004) course at Virginia Tech, Blacksburg, VA.

2016 Guest lecture, “Cancer Immunology” for graduate and undergraduate students in the Immunology and Advanced Inflammation Biology (BIOL 4734/5734) course at Virginia Tech, Blacksburg, VA.

2016 Guest lecture, “Inflammation as an Emerging Hallmark of Cancer” for graduate and undergraduate students in the Immunology and Advanced Inflammation Biology (BIOL 4734/5734) course at Virginia Tech, Blacksburg, VA.

2016 Guest lecture, “Cancer Immunology” for graduate students in the Cancer Diagnostics and Therapeutics (BMES 5984) course at Virginia Tech, Blacksburg, VA.

2017 Guest lecture, “Cancer Immunity” for graduate students in the Fundamentals of Cancer (TBMH 5024) course at Virginia Tech, Blacksburg, VA.

2017 Guest lecture, “Tumor Microenvironment” for graduate students in the Fundamentals of Cancer (TBMH 5024) course at Virginia Tech, Blacksburg, VA.

2017 Guest lecture, “Immune Cells and Crosstalk: Introduction to Immunology” for graduate students in the Translational Biology, Medicine, and Health (TBMH 5004) course at Virginia Tech, Blacksburg, VA.

2017 Guest lecture, “Inflammation and Cancer” for graduate and undergraduate students in the Immunology and Advanced Inflammation Biology (BIOL 4734/5734) course at Virginia Tech, Blacksburg, VA.

2017 Guest lecture, “Advances in Immunotherapeutics” for graduate and undergraduate students in the Advanced Applications in Molecular Life Sciences (BCHM 4784/5784) course at Virginia Tech, Blacksburg, VA.

2017 Guest lecture, “Immune Function in the Intestinal Tract” for graduate students in the Molecular Aspects of Nutrition and Disease (HNFE 5144) course at Virginia Tech, Blacksburg, VA.

2018 Guest lecture, “Immune Cells and Crosstalk: Introduction to Immunology” for graduate students in the Translational Biology, Medicine, and Health (TBMH 5004) course at Virginia Tech, Blacksburg, VA.

2018 Guest lecture, “Diet, Inflammation, and Cancer” for graduate students in the Molecular Aspects of Nutrition and Disease (HNFE 5144) course at Virginia Tech, Blacksburg, VA.

2018 Guest lecture, “Tumor Immunology and Immunotherapy” for undergraduate students in the Cancer Biology (BIOL 4874) course at Virginia Tech, Blacksburg, VA.

2019 Guest lecture, “Cancer Immunology” for graduate and undergraduate students in the Immunology and Advanced Inflammation Biology (BIOL 4734/5734) course at Virginia Tech, Blacksburg, VA.

2019 Guest lecture, “Inflammation as an Emerging Hallmark of Cancer” for graduate and undergraduate students in the Immunology and Advanced Inflammation Biology (BIOL 4734/5734) course at Virginia Tech, Blacksburg, VA.

2020 Evaluator, for Medical Students in the Methods in Logic course at the VTCSOM, Roanoke, VA

2020 Guest lecture, “The Tumor Microenvironment” for graduate and undergraduate students in the Immunology and Advanced Inflammation Biology (BIOL 4734/5734) course at Virginia Tech, Blacksburg, VA.

2020 Guest lecture, “Immuno-Oncology” for graduate and undergraduate students in the Immunology and Advanced Inflammation Biology (BIOL 4734/5734) course at Virginia Tech, Blacksburg, VA.

2021 Guest lecture, “SARS – Innate Immunity” for graduate students in the COVID-19 (SARS-CoV-2) (BMVS 5984) course at Virginia Tech, Blacksburg, VA.

2021 Guest lecture, “COVID-19 Immunology” for undergraduate students in the Science of COVID-19 (BIOL 2984) course at Virginia Tech, Blacksburg, VA.

2021 Guest lecture, “COVID-19 Vaccines” for undergraduate students in the Science of COVID-19 (BIOL 2984) course at Virginia Tech, Blacksburg, VA.

2022 Guest lecture, “The Tumor Microenvironment” for graduate and undergraduate students in the Immunology and Advanced Inflammation Biology (BIOL 4734/5734) course at Virginia Tech, Blacksburg, VA.

2023 Guest lecture, “The Tumor Microenvironment” for graduate and undergraduate students in the Immunology and Advanced Inflammation Biology (BIOL 4734/5734) course at Virginia Tech, Blacksburg, VA.

2023 Guest lecture, “Immuno-Oncology Considerations Following Local Tumor Ablation” for graduate and undergraduate students in the Knives, Needles, and Fields – An Introduction to Surgical and Interventional Oncology (BMES 4984/5984) course at Virginia Tech, Blacksburg, VA.

TEACHING CERTIFICATIONS AND PROFESSIONAL DEVELOPMENT:

2007 Certificate in College Teaching, UNC Chapel Hill

2014 Master Online Instructor Certificate, Technology-enhanced Learning and Online Strategies, Virginia Tech

2014 Networked Learning and Design Strategies Faculty Showcase, “Principles of Biomedical and Health Science Research”, On-Line Course Development, TLOS, Virginia Tech, Blacksburg, VA.

JUNIOR FACULTY MENTORSHIP: 3 Junior Faculty Members

STUDENT MENTORSHIP:

MAJOR ADVISOR OF CURRENT GRADUATE STUDENTS:

PhD Mentor Biomedical and Veterinary Science: 2 Students
PhD Mentor Program in Translational Biology, Medicine, and Health: 3 Students
MD Research Mentor: 3 Students

MAJOR ADVISOR OF FORMER GRADUATE STUDENTS:

Post-Baccalaureate Research and Education Program (PREP) Students: 3 Students
Biomedical and Veterinary Science: 8 Students
Program in Translational Biology Medicine and Health: 5 Students
MD Research Mentor: 2 Students
Summer Veterinary Research Program: 9 Students

THESIS AND DISSERTATION COMMITTEE SERVICE: 47 Students

UNDERGRADUATE STUDENT RESEARCH MENTORSHIP: 50 Students

HIGH SCHOOL STUDENT MENTORSHIP: 1 Student

LABORATORY TECHNICIAN SUPERVISION: 3 Laboratory Technicians

IRVING ALLEN'S TESTIMONY HISTORY

Irving Coy Allen

List of Former Testimony

1. Remote Videotaped Deposition taken on June 30, 2023, in "Leonard A. Peters and Aileen H.N. Peters vs. Monsanto Company, a Delaware corporation; and Does 1 to 25," Case No. 1CCV-20-0001623 JMT, in the Circuit Court of the First Circuit, State of Hawaii, by RPR, RMR, CMRS, CRR, CSR Sheila Moore;

2. Trial Testimony taken on November 15, 2023 (AM & PM) and November 16, 2023 (AM & PM), in "Kelly J. Martel vs. Monsanto Company, et al.," No. 0008, in the Court of Common Pleas, First Judicial District of Pennsylvania, by CRR, RMR, CCR Meta Kelly;

3. Remote Videotaped Deposition taken on March 5, 2024, in "Jeanne Brazell et al. v. Monsanto Company," Case No. 1922-CC11327, in the Circuit Court of St. Louis City, Missouri, by CR, Notary Public Katherine S. Hruneni;

4. Remote Videotaped Deposition taken on June 7th, 2024 in "Amy Ross, individually and as personal representative of the estate of Timothy J. Ross v. Liberty Mutual Insurance Co., and Century Indemnity Co.," Case No. 2184-CV-02212 BLS1, in the Superior Court of the Commonwealth of Massachusetts, by CR, Notary Public Kimberly L. Ribaric;

5. Remote Videotaped Deposition taken on July 24th, 2024 in "Neal Allen Hayden and Robin D. Hayden v. Monsanto Company, Case 3:19-cv-05600-VC; The Estate of Caryl Ann Haase and Clyde Edward Haase v. Monsanto Company, Case 3:19-cv-05957-VC; Carol Ann Huntley v. Monsanto Company, Case 3:19-cv-06407-VC; Kenneth Noel Eilmes, Jr. and Kelleen Patrice Eilmes v. Monsanto Company, Case 3:19-cv-05345-VC, in the United States District Court of Norther District of California, by CR, Notary Public Denise Dobner Vickery