CDMRP
DEPARTMENT OF DEFENSE
CONGRESSIONALLY DIRECTED
MEDICAL RESEARCH PROGRAMS

Peer Reviewed Cancer Research Program

Advancing the Future of Cancer Research

For more information, please visit
cdmrp.health.mil/prcrp

VISION: To advance mission readiness of U.S. military members affected by cancer

MISSION: To successfully promote high-impact research in cancer prevention, detection, treatment, quality of life and survivorship for Service Members, their Families, Veterans and the American public

APPLICATION REVIEW PROCESS:

The CDMRP uses a two-tier review process for evaluating applications. The first tier of evaluation is a scientific peer review of the applications, where applications are measured against established criteria for determining scientific merit. The second tier is a programmatic review conducted by the Programmatic Panel, which is composed of leading scientists, clinicians and consumers. The Programmatic Panel compares applications to each other and makes recommendations for funding based on scientific merit, potential impact, adherence to the intent of the award mechanism, relevance to program goals and portfolio composition.

CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

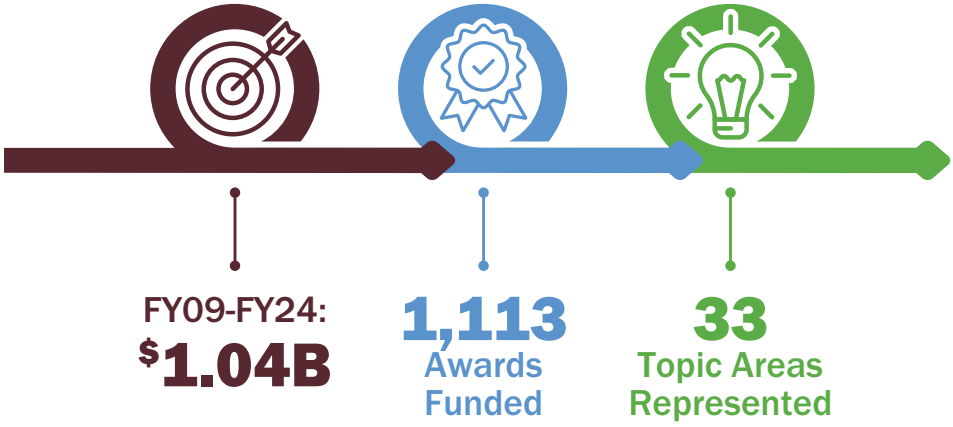
Congress established the CDMRP in 1992 from a grassroots effort led by the breast cancer advocacy community. That effort resulted in a congressional appropriation of funds for breast cancer research and initiated a unique partnership among the public, Congress and the military. Since then, the CDMRP grew to encompass multiple targeted programs and managed over $22.3 billion in congressional special interest funds from its inception through FY24. Congress provides overarching intent for each individual CDMRP program and specifies funding as part of the annual DOD appropriations bill.

PEER REVIEWED CANCER RESEARCH PROGRAM

BACKGROUND

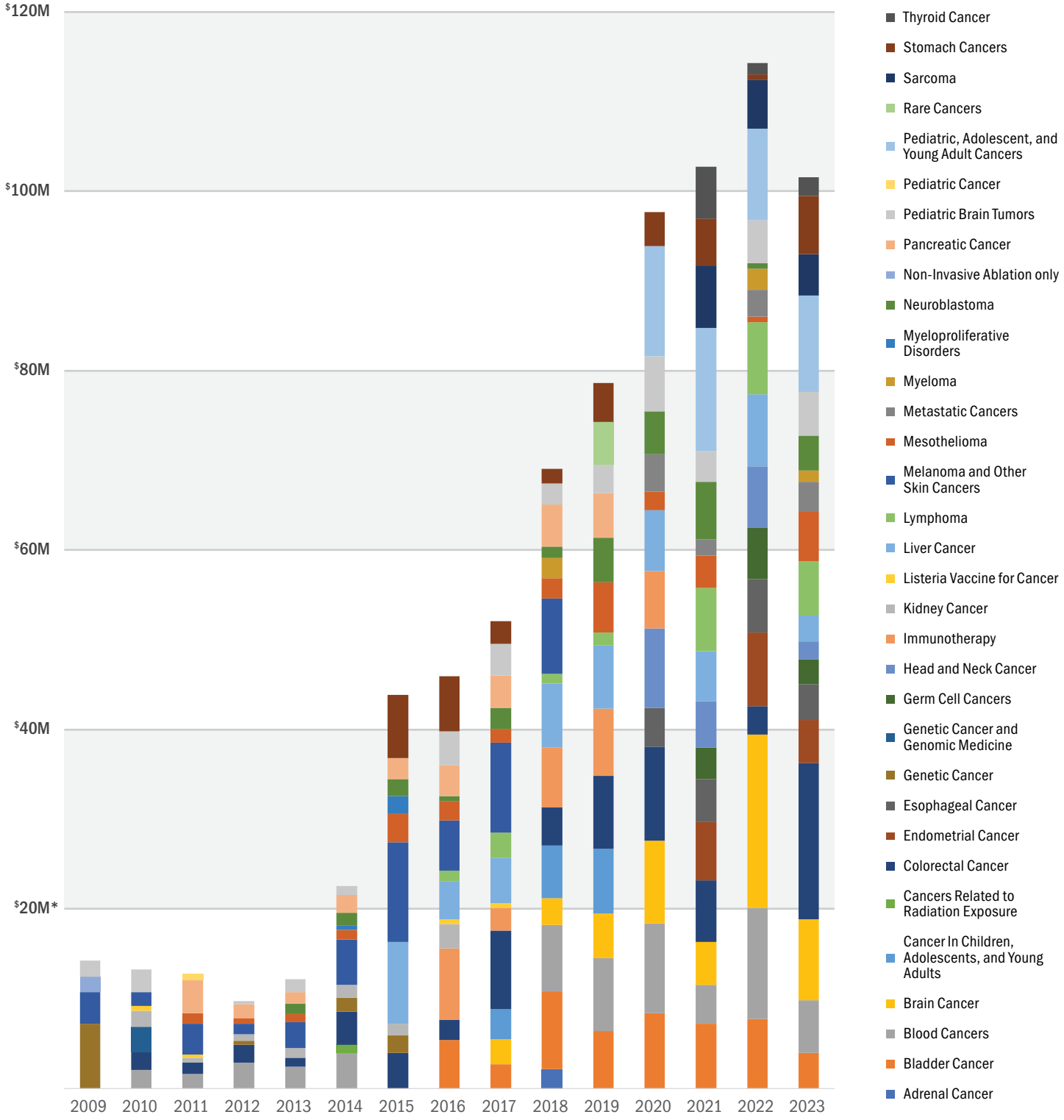
Congress established the PRCRP as a multi-topic program in FY09 to support innovative and impactful cancer research relevant to Service Members and their Families. From FY09 through FY24, the PRCRP invested $1.04B in congressional appropriations for cancer research covering 33 unique topic areas. The PRCRP challenges the research community to address the increased cancer risk Service Members face due to exposures related to military service and deployments and reduce cancer's negative impact to military readiness. To accomplish those goals, the PRCRP funds projects along the entire research continuum, from bench to bedside, targeting the gaps in the cancer research landscape in the program's topic areas.

CONGRESSIONAL APPROPRIATIONS



PRCRP CONGRESSIONAL APPROPRIATIONS/TOPIC AREAS

The PRCRP funds a variety of cancer topic areas based on congressional language. In its inaugural year, the PRCRP offered four topic areas. Since then, the PRCRP funded 33 different topic areas. It is important to note that congressional language designates the topic areas, and topic areas may change from year to year.



FY09-FY23 PRCRP Funding History and Awards Made
**Millions*

ADVANCING THE UNDERSTANDING OF CANCER RISK IN SERVICE MEMBERS

Congressional language directs the PRCRP to fund research relevant to Service Members and their Families. The PRCRP crafts it's investment strategy around the requirement to maintain relevance to military health concerns such as the risk of certain cancers occurring due to exposure related to military service and deployment. Other cancers may affect the military in that a diagnosis will impact mission readiness. All applications submitted to and funded by the PRCRP must show relevance to military health. In FY24, there are two military health focus areas.

PRCRP FY24 Military Health Focus Areas

- Environmental exposure risk factors associated with cancer
- Mission Readiness and Gaps in Cancer Research

Occupational and environmental hazards may increase the risk of developing certain cancers as shown in the table below.

Environmental or Occupational Exposure-Related Cancer Risks

Risk	Related PRCRP Topic Area/Cancer
Agent Orange and Other Herbicides[1]	Bladder cancer, chronic lymphocytic leukemia, Hodgkin's and non-Hodgkin's lymphoma, multiple myeloma, soft tissue sarcoma
Asbestos[2]	Colorectal cancer, esophageal cancer, laryngeal cancer, mesothelioma, pharyngeal cancer, stomach cancer
Radiation[3,4]	Bone cancers, bladder cancer, brain cancer, colorectal cancer, endometrial/uterine cancers, esophageal cancer, leukemias (except chronic lymphocytic leukemia), liver cancer, lymphoma (except Hodgkin's lymphoma), multiple myeloma, salivary gland, stomach cancer, thyroid cancer
Infectious Agents[5]	**Epstein-Barr virus:** Lymphoma, oral cavity, stomach cancer; **Helicobacter pylori:** Gastric cancer; **Hepatitis B and hepatitis C viruses:** Liver cancer; **Human papilloma virus:** Anogenital cancer, head and neck cancer, uterine cancer; **Schistosoma haematobium:** Bladder cancer
Industrial Solvents[6]	Adrenal cancer, blood cancers (leukemia, lymphoma), bladder cancer, bone cancers, brain cancer, gastric cancer, liver cancer, nasopharyngeal cancer
Chemical Weapons[7]	Acute myeloid leukemia, laryngeal cancer, nasopharyngeal cancer

[1] https://www.publichealth.va.gov/exposures/agentorange/conditions/index.asp
[2] https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=30&tid=4
[3] https://www.nrc.gov/about-nrc/radiation/health-effects/rad-exposure-cancer.html
[4] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2859619/
[5] https://www.atsu.edu/faculty/chamberlain/InfectiousDiseaseAgentsCauseCancer.htm
[6] https://www.publichealth.va.gov/exposures/solvents/index.asp
[7] https://www.publichealth.va.gov/exposures/mustardgas/

PRCRP-FUNDED RESEARCH STUDYING MILITARY POPULATIONS

Uncovering the Long-Term Impact of Oropharyngeal Cancer and Dysphagia on Dietary Quality and Nutrition Among Veteran Cancer Survivors: The U-DINE Study

Marcia Otto, Ph.D., University of Texas, Health Science Center at Houston

PRCRP Topic Area: Head and Neck Cancer

Patients with oropharyngeal cancer, OPC, often experience swallowing difficulties that lead to changes in eating patterns and potential for low quality diets and increase risk of chronic disease and premature death after cancer treatment.[1,2] Otto and her group plan to examine diet patterns among OPC patients during the acute, extended and permanent stages of cancer survivorship. This project is in collaboration with Kate Hutcheson, Ph.D., at MD Anderson Cancer Center, Vlad Sandulache, M.D., Ph.D., at Baylor College of Medicine and Michael E. DeBakey at the Veterans Affairs Medical Center.

Thyroid Cancer Aggressiveness in Agent Orange-Exposed Veterans

Maaike Van Gerwen, Ph.D., Icahn School of Medicine at Mount Sina

PRCRP Topic Area: Thyroid Cancer

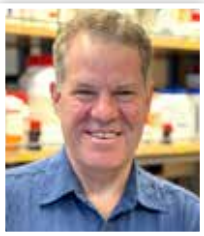
2,3,7,8-tetrachlorodibenzo-p-dioxin, a contaminant present in the defoliant Agent Orange used during the Vietnam War, is thought to be a human carcinogen associated with increased risk of thyroid cancer. This study seeks to investigate whether 2,3,7,8-tetrachlorodibenzo-p-dioxin exposure corresponds to more aggressive thyroid cancer features, including higher rates of metastasis, genetic modifications and cancer recurrence, as well as lower survival.

Non-Endoscopic Screening to Impact Esophageal Cancer in Veterans

Katarina Greer, M.D., Cleveland VA Medical Research & Education Foundation

PRCRP Topic Area: Esophageal Cancer, Clinical Trial

This study evaluated the use of EsoCheck a non-endoscopic esophageal balloon sampling device, coupled with EsoGuard, a DNA-based screening assay. Greer and her team evaluated the efficacy of this treatment in a Veteran population with Barrett's esophagus and found that the Esocheck and Esoguard coupled sampling showed high overall sensitivity, tolerance and acceptability. Greer and her team applied for and received an FY23 PRCRP Impact Award – Clinical Trial Option to further this work. More information can be found on Page 17.



Translational Impact of Electrophile Adducts in Colorectal Cancer

Keith Wilson, M.D., Vanderbilt University Medical Center

PRCRP Topic Area: Colorectal Cancer

Colorectal Cancer may evolve from inflammatory bowel disease, IBD. IBD prevalence is especially high in U.S. Veterans due to deployment-associated exposures to environmental chemicals and pathogens, changes to the microbiome and post-traumatic stress disorder. Wilson and his team plan to use biopsy samples from colitis patients and normal controls to determine if electrophiles produced during colitis play a key role in IBD and colitis-associated cancers. They will further investigate these electrophiles as markers of colorectal cancer risk and potential chemoprevention targets in patients with chronic colitis.

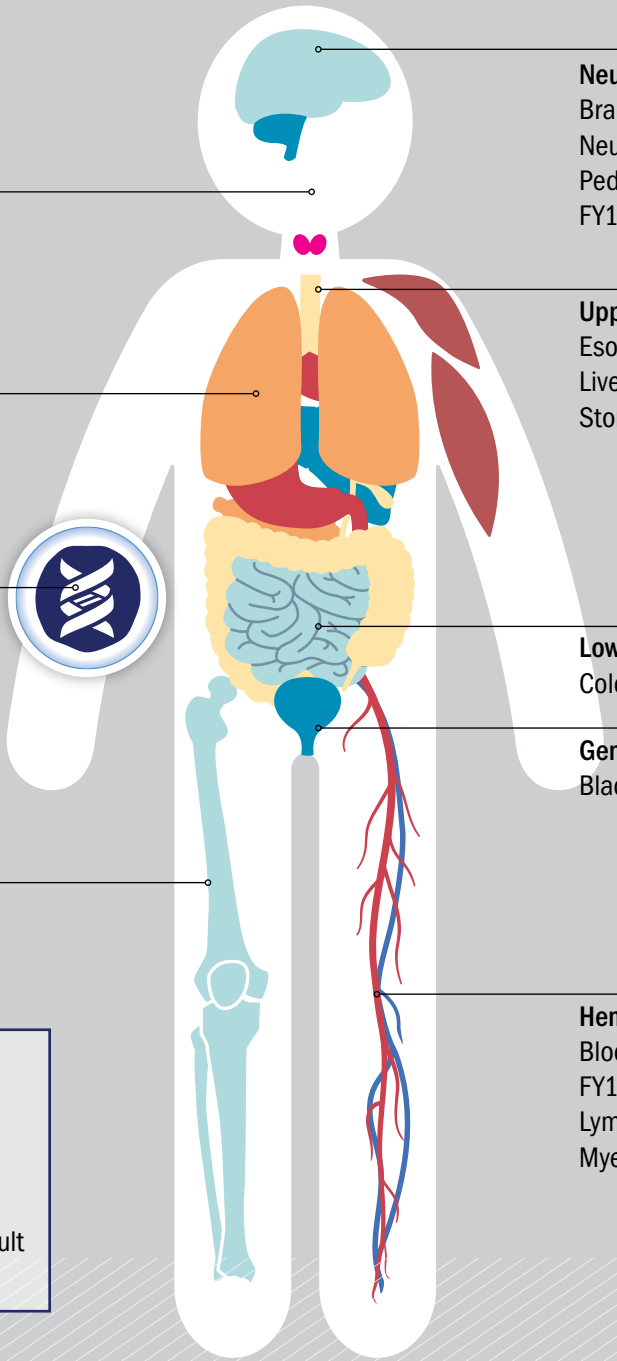
References:

[1] M.M. Szczesniak et al. "Persistent Dysphagia After Head and Neck Radiotherapy: A Common and Under-Reported Complication With Significant Effect on Non-Cancer-Related Mortality," *Clinical Oncology (R Coll Radiol)* 11, (2014):697-703. doi: 10.1016/j.clon.2014.08.009.

[2] M. Kamal et al. (MD Anderson Head and Neck Cancer Symptom Working Group). Modeling symptom drivers of oral intake in long-term head and Neck Cancer Survivors. *Support Care Cancer* 4 (2019):1405-1415. doi: 10.1007/s00520-018-4434-4.

PRCRP TOPIC AREAS FY20–FY24

The PRCRP congressional language and topic areas are designated yearly by Congress. While the list of topics may differ from one year to the next, many topic areas have consistently been included in the PRCRP for years. Some PRCRP topic areas are not specific cancers or types of cancers, but areas related to cancer research such as Immunotherapy, or specific populations such as Young Adults, an age that includes many Service Members.



Neurologic Cancers
Brain Cancer (FY17–FY24)*
Neuroblastoma (FY13–FY24)
Pediatric Brain Tumors (FY09–FY10; FY12–FY14; FY16–FY24)

Head and Neck Cancers
Head and Neck Cancer (FY20–FY23)
Thyroid Cancer (FY21–FY24)

Upper Gastrointestinal Cancer
Esophageal Cancer (FY20–FY24)
Liver Cancer (FY15–FY24)
Stomach Cancer (FY15–FY24)

Thoracic Cancer
Mesothelioma (FY11–FY24)

Reproductive Oncology
Germ Cell Cancer (FY21–FY24)
Endometrial Cancer (FY21–FY24)
Von Hippel–Lindau Syndrome Malignancies (FY22–FY23)

Lower Gastrointestinal Cancer
Colorectal Cancer (FY10–FY24)

Genitourinal Cancer
Bladder Cancer (FY16–FY24)

Musculoskeletal Cancer
Sarcoma (FY21–FY24)

Hematologic Cancers
Blood Cancer (FY09–FY14; FY18–FY24)
Lymphoma (FY16–FY19; FY21–FY24)
Myeloma (FY18; FY22–FY24)

Special Topics
Immunotherapy (FY16–FY20)
Metastatic Cancers (FY20–FY24)

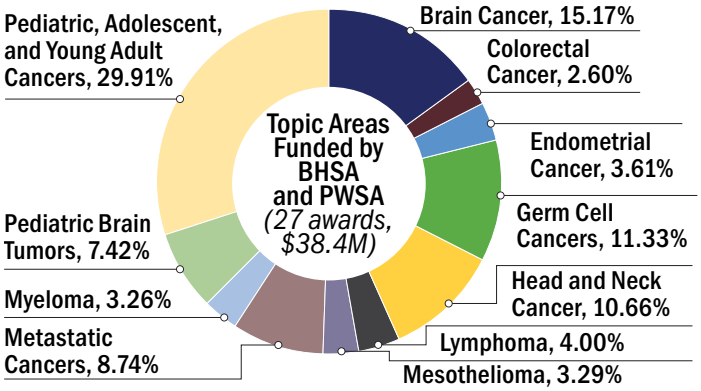
Special Populations
Pediatric, Adolescent and Young Adult Cancers (FY17–FY24)**

**The Brain Cancer topic area excluded applications studying glioblastoma in FY24 following the creation of the Glioblastoma Research Program.*

***For FY17–FY19 this topic area was designated "Cancer in Children, Adolescents and Young Adults."*

EMPOWERING SURVIVORSHIP AND ENHANCING PATIENT OUTCOMES

There are approximately 18.1 million cancer survivors in the United States, and this number is projected to increase by 24.4% in 10 years.[1] Understanding survivorship needs and filling research gaps in the psychological health and well-being of those affected by cancer (e.g., patients, family members) present an immediate unmet need.



In FY20, the PRCRP introduced a new initiative to fund research focused on patient well-being and survivorship through the release of the Behavioral Health Science Award, or BHSA. This was followed in FY23 by the Patient Well-Being and Survivorship Award, or PWSA. These funding opportunities support innovative research to advance studies in preservation of function, quality of life, symptom management, resilience, relief from neurocognitive deficits and support for psychosocial issues related to cancer diagnosis, treatment and survivorship.

Selected PRCRP-Funded Behavioral Health Science Awards and Patient Well-Being and Survivorship Awards:

Impact of Platinum-Related Hearing Loss on Quality of Life and Educational Attainment in Germ Cell Tumor Survivors

Jenny Poynter, Ph.D., University of Minnesota - Twin Cities | PRCRP Topic Area: Germ Cell Cancer

Germ cell tumors are cancers of the reproductive system with more than 900[2] children and adolescents newly diagnosed per year in the United States and are the most common type of cancer in young adult men. After treatment, patients may experience late effects such as ototoxicity or hearing loss, neuropathy, cardiac disease, second malignancies and infertility. To better understand long-term adverse effects of the standard germ cell tumor chemotherapy treatment regime and quality of life issues, Poynter is establishing a comprehensive survivorship study of germ cell tumor patients between the ages of 0 and 19 years to examine the impact of treatment-associated hearing loss and neuropathy on educational attainment and quality of life.

Transforming Radiation Therapy to Preserve Neurocognition in Children with Brain Tumors

Sahaja Acharya, M.D., Johns Hopkins University | PRCRP Topic Area: Pediatric, Adolescent and Young Adult Cancers

Neurocognitive impairment is a well-established late effect of radiation therapy for pediatric brain tumor patients and can affect academic performance, social-emotional functioning and the ability to live independently as an adult. Acharya initiated a pilot study in pediatric brain tumor patients limiting radiation dose to the hippocampus, corpus callosum and frontal white matter to characterize early neurocognitive outcomes. A second arm of the study will characterize late neurocognitive outcomes in pediatric brain tumor survivors who completed radiation therapy more than two years ago to interrogate the relationships between radiation dose, white matter injury and neurocognition. If successful, this project could shift the paradigm of how radiation therapy is administered, where both tumor control and neurocognitive outcomes are optimized and potentially improve short- and long-term quality of life.

Improving Psychosocial Support for Mesothelioma Caregivers Through a Participant-Centered Online Support Group

Amanda Woodward, Ph.D., Michigan State University | PRCRP Topic Area: Mesothelioma

Current treatments for mesothelioma are only marginally effective, and half of all patients die within a year of diagnosis. Caregivers struggle with fear, anxiety, depression and anger while caring for their loved one. To date, there is very little research focused on mesothelioma caregivers. Woodward's project aims to improve understanding of the experience of mesothelioma caregivers from their loved one's diagnosis, through the patient's death and the period of bereavement that follows. The team plans to conduct one-on-one interviews and focus groups with patients, caregivers, bereaved and health care professionals. The knowledge gained from this project will be used to develop an online support intervention.

References:

[1] American Cancer Society. Cancer Treatment and Survivorship Facts & Figures 2022-2024. Atlanta: American Cancer Society; 2022.

[2] F. Shaikh et al. "Paediatric Extracranial Germ-Cell Tumours." *Lancet Oncol* 17, no. 4 (2016):e149-e162. doi: 10.1016/S1470-2045(15)00545-8.

RESEARCH HIGHLIGHTS

Radiomics-Based Companion Diagnostic for Predicting and Assessing Response to Chemoradiation in Rectal Cancers

Satish Viswanath, Ph.D., Case Western Reserve University

Topic Area: Colorectal Cancer | Award Mechanism: FY15 Career Development Award and FY20 Idea Award

Colorectal cancer is the second most common cause of cancer-related deaths in the United States.[1] Between 1997 and 2016, there were 1,108 cases of colorectal cancer diagnoses among Service Members aged 20 to 59 years, and the Veterans Affairs Central Cancer Registry reported 15,205 Veterans diagnosed with colorectal cancer between 2009 and 2012.[2,3] The standard of care treatment for rectal cancer includes neoadjuvant therapy in the form of chemoradiation, to shrink the tumor, followed by a total excision.[4] Magnetic resonance imaging, or MRI, is routinely used pre- and post-chemoradiation to noninvasively assess the tumor; however, restaging of the tumor post-chemoradiation is often difficult due to the difficulties in visual identification of residual tumor on imaging. Thus, researchers and clinicians need more accurate imaging markers for improving noninvasive evaluation of the rectal tumor.

With an FY15 Career Development Award, Viswanath sought to develop a computerized prediction tool to identify residual disease during the post-chemoradiation therapy MRI to better assess rectal cancers prior to surgery. The team successfully characterized the rectal environment through assessment of radiomic features and predicted and evaluated chemoradiation responses. Their prediction model successfully identified 80% of chemoradiation nonresponders in presurgery MRI, as well as identify reduction of tumor size with 80% sensitivity.

Building on this work, Viswanath received an FY20 Idea Award to develop a computerized imaging-based companion diagnostic to identify which rectal cancer patients will benefit from chemoradiation. His research facilitates his ongoing collaboration between his institution, Case Western Reserve University and three major medical centers, University Hospitals Cleveland, Cleveland Clinic and the Cleveland VA Medical Center. Using baseline and follow-up MRIs, pathologic outcomes and clinical information, the team plans to construct the imaging tools using data from two of the institutions. The team will use data from the third institution to validate the tool's effectiveness.

Viswanath and his team successfully illustrated the potential utility of radiomics and machine learning in cancer care. Their work successfully developed a model that, if validated, could determine colorectal patient response to chemoradiation. The outcomes of their research could prevent unnecessary surgical procedures or provide improved guidance to providers during surgery through more accurate identification of residual disease. Additionally, the model's ability to discern nonresponders could potentially reduce the risk of continued cancer growth and radiation injury. The technology potentially gives providers new tools when developing treatment plans and could improve the quality of life for cancer patients and survivors.

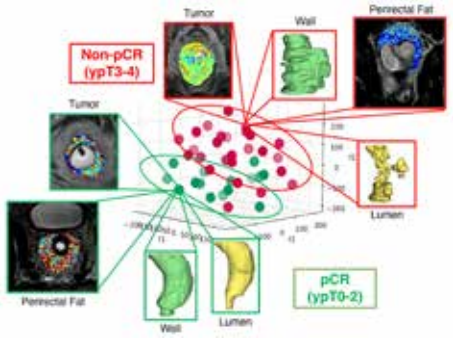


Figure 1: *AI-based image features capturing morphologic disruptions and heterogeneity within and around the lesion on MRI can accurately distinguish responders (green) from non-responders (red) after chemoradiation; seen via scatter plot of top-ranked radiomic features from tumor, rectal wall, perirectal fat, and lumen.*

Figures Provided by the Principal Investigator

References:

[1] R.L. Siegel et al. "Colorectal Cancer Statistics., 2023" *CA Cancer J Clin 73*, no. 3 (2023):233-254. doi: 10.3322/caac.21772.

[2] S. Stahlman and A. Oetting. "Age-Period-Cohort Analysis of Colorectal Cancer, Service Members Aged 20-59 Years, Active Component, U.S. Armed Forces, 1997-2016." *MSMR 24*, no.7 (2017):12-19.

[3] L.L. Zullig et al. "Colorectal Cancer Statistics From the Veterans Affairs Central Cancer Registry," *Clin Colorectal Cancer* e199-e204.

[4] B.D.P. O'Neill et al. "Non-Operative Treatment After Neoadjuvant Chemoradiotherapy for Rectal Cancer," *Lancet Oncol* 8, no.7 (2007):625-633.

Publications:

J.T. Antunes et al. "RADIomic Spatial TexturAl descripTor (RADISTAT): Quantifying Spatial Organization of Textural Heterogeneity on Imaging Associated With Tumor Response to Treatment," *Journal of Biomedical and Health Informatics* 26, no.6 (2022):2627-2636.

C. Alvarez-Jimenez et al. "Radiomic Texture and Shape Descriptors of the Rectal Environment on Post-Chemoradiation T2-Weighted MRI Are Associated With Pathologic Tumor Stage Regression in Rectal Cancers: A Retrospective, Multi-Institution Study," *Cancers (Basel)* 12, no. 8 (2020):2027.

Neuroblastoma: Modified Natural Killer Cells to Improve Immunotherapy

Catherine M. Bollard, M.D., M.B.B.C.H., Children's National Research Institute

Topic Area: Neuroblastoma | Award Mechanism: FY14 Idea Award with Special Focus

Neuroblastoma, a cancer of developing nerve cells, most commonly affects children under the age of five.[1] Patients who do not respond to chemotherapy urgently need alternate approaches. One potential strategy is immunotherapy, a treatment method that uses the body's immune system to target and kill tumor cells. Some antitumor immunotherapies employ natural killer, or NK, cells. NK cells are immune cells that circulate throughout the body and attack abnormal cells, including cancer cells, when encountered. However, many tumors evade immunotherapy by secreting an immunosuppressive molecule such as the cytokine TGFβ.

With an FY14 Idea Award with Special Focus, Bollard and her team sought to improve immunotherapy by engineering NK cells that resist TGFβ while also increasing the cell's antitumor activity. Many immunotherapies use the patient's own immune cells, but cancer patients' peripheral blood NK cells are generally scarce, with limited killing activity in the tumor environment, and have a short longevity of approximately two weeks. To overcome these issues, Bollard's team engineered NK cells harvested from umbilical cord blood to express a mutant TGFβ receptor, protecting the cells from TGFβ-related inhibitory effects. NK cells derived from umbilical cord blood contain certain features that allow them to persist longer in the body than similar cells harvested from donor or patient blood.

Bollard's team treated mice with unmodified or modified NK cells over the course of 28 days, a length of time which mimics the treatment regimen often used for neuroblastoma in the clinic. The team measured the cell activity and evaluated tumor growth as well as overall survival. Results indicate that mice treated with modified NK cells experienced the best outcomes overall, with the slowest tumor growth and longest survival, presumably because the suppressive effects of TGFβ protect the modified NK cells.[2]

The project's results successfully demonstrate the novel strategy of collecting NK cells from umbilical cord blood and the potential benefits of this approach. As with many treatments derived from donors, NK cells need to be matched to their recipient to ensure that they will correctly distinguish healthy cells from cancerous cells; finding matches can be especially challenging for certain ethnic minority groups. There are over 500,000 banked units of umbilical cord blood worldwide, providing a large pool of prospective matches for patients in need of NK cell therapy. In addition, although the NK cells in Bollard's studies were tested in models of neuroblastoma, they could impact immunotherapy for many cancers should they reach clinical use. Tumors of mesothelioma, pancreatic cancer, melanoma and other cancers secrete TGFβ, making them potential candidates for immunotherapy with modified NK cells. Currently, this work is moving forward toward the clinic through multiple avenues. Bollard received funding via Cancer Research UK and the National Cancer Institute's "Cancer Grand Challenges;" part of this project will further develop the TGFβ component to make pediatric solid tumors more vulnerable to immunotherapy. Additionally, the engineered NK cells have been licensed to a biotech company for further development.

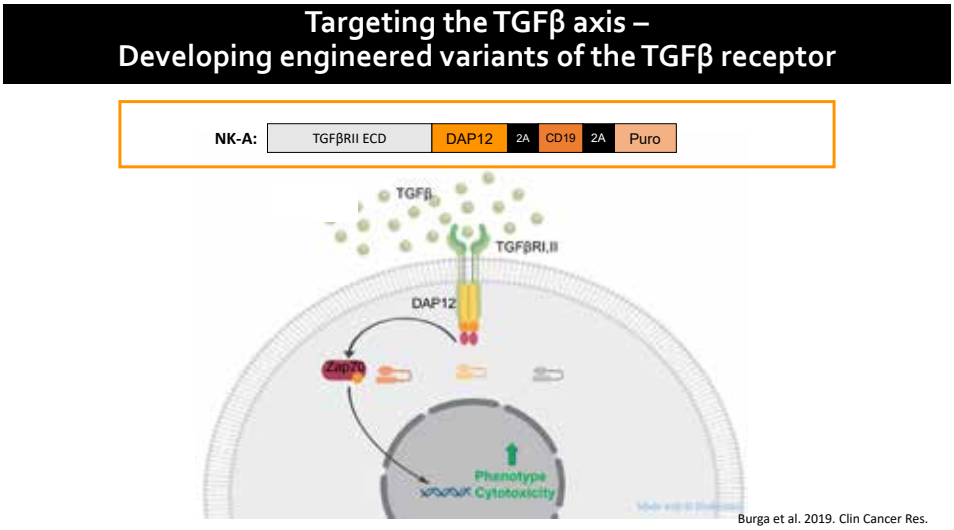


Figure 2: *This figure illustrates the novel variant TGFβ receptor coupling with the TGFβ dominant negative receptor to the DNAX-activation protein 12 (DAP12) NK activation motif, which initiates signaling through its single immunoreceptor tyrosine-based activation motif (ITAM), with the aim of enhancing NK cell activation after ligand binding (Figure adapted from Burga et al, Clinical Cancer Research 2019).*

Figures Provided by the Principal Investigator

Reference:

[1] American Cancer Society. About Neuroblastoma. Accessed April 11, 2023, https://www.cancer.org/cancer/neuroblastoma/about.html

Publication:

R.A. Burga et al. "Engineering the TGFβReceptor to Enhance the Therapeutic Potential of Natural Killer Cells as an Immunotherapy for Neuroblastoma," *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research,*" 25, no. 14 (2019):4400-4412. https://doi.org/10.1158/1078-0432.CCR-18-3183.

Tumor-Specific Lymphoma Organoids for Understanding the MALT1 Pathway for Targeted Drug Therapies

Ankur Singh, Ph.D., Cornell University

Topic Area: Lymphoma | Award Mechanism: FY16 Career Development Award

Lymphoma, a type of cancer, develops when immune cells present in the blood grow uncontrollably. According to the Leukemia and Lymphoma Society, diffuse large B cell lymphoma, or DLBCL, is one of the most prevalent forms of the cancer, accounting for 25% of all lymphoma cases in the United States.[1] B cells are functionally diverse immune cells; as a result, when DLBCL develops, the cancer cells are made up of several different populations of malignant cells, making effective treatment difficult.

Currently, the lack of cellular models to accurately represent DLBCL and its tumor microenvironment make it difficult to assess the mechanisms driving the cancer's progression and develop effective targets for treatment. Singh received an FY18 PRCRP Career Development Award and developed three-dimensional, or 3D, cell models, referred to as organoids, and used them to examine pathways in the tumor microenvironment that drive tumor growth and may provide therapeutic benefit through inhibition.

To develop an organoid model that accurately represented human DLBCL, Singh used previously collected data from 1,000 patient samples to determine signals in the proteins and molecules surrounding the lymphoma cells. The team identified several integrins, proteins important for adhesion of cells, that increased DLBCL cell survival, and found these integrins are expressed at varying levels, suggesting multiple factors may play a role in the tumor microenvironment. Using this data, several integrin-specific organoids were developed.

The physical characteristics, or phenotype, of the different integrin-specific organoids were assessed by comparing the two-dimensional, or 2D, DLBCL cell lines and the DLBCL organoids. The team found the interaction of integrins with the 3D environment led to increased expression of B cell receptors, surface proteins important to activation and subsequent growth and expansion of B cells. In addition, varying sizes of DLBCL organoids were grown and showed that organoid size also effected the phenotype of DLBCL cells and varied depending on the integrin expression.

Next, the team developed a device and processes to produce 3D DLBCL cultures expressing integrins in bulk. For the organoids to be useful for experimentation they must be viable for more than 15 days. The team was able to produce a DLBCL organoid that could be cultured for 28 days by analyzing and optimizing variables such as pH and starting cell density.

Singh began evaluation of pathways and inhibitors with therapeutic potential using long-term cultures of DLBCL organoids. They identified mucosa-associated lymphoid tissue lymphoma translocated protein 1 or MALT1, a protein that activates the nuclear factor kappa B pathway, which regulates B cell survival and plays a role in development of cancer. Inhibition of MALT1 was able to be assessed like never before in the newly developed organoids. The new model system will aid the team in identifying genes and other factors associated with DLBCL and its tumor microenvironment, which play a role in disease progression and may be targetable for treatment. The successful development of DLBCL organoids that more accurately represent the characteristics of the cancer has the potential to lead to new treatment discoveries.

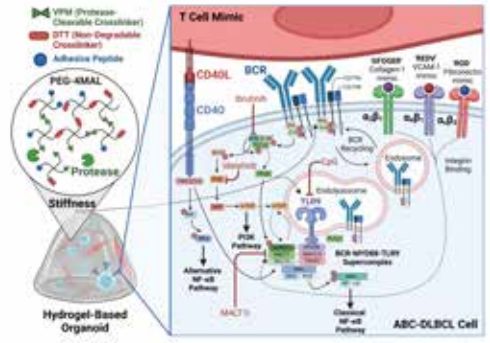


Figure 3: *Synthetic hydrogel-based lymphoma organoids to evaluate the impact of cellular and biophysical cues on B cell receptor (BCR) signaling. Incorporating engineered stromal T-cell mimics and integrin-binding peptides modulated multiple oncogenic pathways, including MALT-1, which can only be overcome with combined targeted therapies (Created using BioRender.com).*

Figures Provided by the Principal Investigator

Reference:

[1] Leukemia and Lymphoma Society. Diffuse Large B-Cell Lymphoma (DLBCL). https://www.lls.org/research/diffuse-large-b-cell-lymphoma-dlbcl

Publications:

L. Fontan et al. "Identification of MALT1 Feedback Mechanisms Enables Rational Design of Potent Anti-Lymphoma Regimens for ABC-DLBCL," *Blood* 137, no. 6 (2021):788-800.

H. Scholze et al. "Combined EZH2 and Bcl-2 Inhibitors as Precision Therapy for Genetically Defined DLBCL Subtypes," *Blood Advances* 4, no. 20 (2020):5226-5231.

S. Kim et al. "Multiscale Engineering of Immune Cells and Lymphoid Organs," *Nature Reviews Materials* 4 (2019):355-378.

M.E. Wechsler et al. "Engineered Microscale Hydrogels for Drug Delivery, Cell Therapy, and Sequencing," *Biomedical Microdevices* 21, no. 2 (2019):31.

F. Apoorva et al. "How Biophysical Forces Regulate Human B Cell Lymphomas," *Cell Reports* 23, no 2 (2018):499-511.

A. Singh et al. "Beyond Tissue Stiffness and Bioadhesivity: Advanced Biomaterials to Model Tumor Microenvironments and Drug Resistance," *Cell: Trends in Cancer* 4, no. 4 (2018):281-291.

Pharmacological Management of Ultraviolet Radiation-Induced Skin Cancer

Nabiha Yusuf, Ph.D., University of Alabama at Birmingham

Topic Area: Melanoma and Skin Cancers | Award Mechanism: FY17 Expansion Award

Ultraviolet B radiation can induce structural breaks in cellular DNA, resulting in what is commonly referred to as lesions. If the body's cellular repair mechanisms can't repair the lesions, the damaged cells will replicate, which can eventually result in skin cancer. Cancerous skin shows an increased expression of toll-like receptor-4 or TLR4, an immune system protein that is important for the activation of inflammatory signaling. However, information regarding its role of tumor progression is lacking. Research demonstrates that a drug called Resatorvid inhibits the activity of TLR4 in the skin of laboratory mice exposed to a single dose of ultraviolet B radiation.

With the help of an FY17 Expansion Award that built upon data from a previously funded FY09 New Investigator Award, Yusuf sought to study the role of TLR4 inhibitor Resatorvid in preventing non-melanoma skin cancer and the mechanism involved in this process. Yusuf and her team began by conducting a series of experiments involving mice treated topically with Resatorvid or non-treated controls that were exposed to ultraviolet B radiation. They discovered that Resatorvid-treated mice had less DNA damage and elevated XPA gene expression. The XPA gene plays an important role in repairing damaged DNA. They determined that Resatorvid regulates the inflammatory response by inhibiting the activation of an inflammation-triggering protein called NLRP3 following ultraviolet B exposure, but only in mice where XPA gene is activated (or "expressed"). They also discovered that Resatorvid inhibits proteins that regulate the immune system called cytokines and interleukins.

Yusuf's team then applied that knowledge to understand how Resatorvid inhibits the growth of ultraviolet B-induced skin tumors. They examined the lymph nodes, spleens and skin tumors of mice exposed to ultraviolet B radiation with and without treatment of topical Resatorvid. Results showed significantly decreased tumor development in Resatorvid-treated mice compared to the non-treated control animals. In addition, they discovered that Resatorvid deactivates certain white blood cells, called regulatory T-cells, that suppress the immune response and bone marrow blood cells that help tumors grow, called myeloid cells. Resatorvid also inhibits the function of an interleukin with potent anti-inflammatory properties called interleukin 10.

The findings from Yusuf's research have potential value for developing clinical trials of new and more effective agents for preventing and treating ultraviolet B-induced non-melanoma skin cancers through a combination of Resatorvid and traditional sunscreens. This development would be particularly beneficial to military personnel, among whom the rates of skin cancer have been increasing for several decades, in part because of their frequent and long-duration exposure to ultraviolet B radiation in the course of their duties.

Publications:

M.A. Sherwani et al. "Toll-like Receptor-4 Antagonist Enhances the Repair of Ultraviolet Radiation-Induced DNA Damage and Augments Antitumor Immune Responses in Mice," *Cancers (Basel)*13 (2021):5406. https://doi.org/10.3390/cancers13215406.

I. Ahmad et al. "Toll-Like Receptor-4 Deficiency Inhibits Ultraviolet Radiation-Induced Tumor Development by Modulation of Immune and Inflammatory Responses," *Molecular Carcinogenesis* 60 (2021):60-70. https://doi.org/10.1002/mc.23271.

The Prevalence and Impact of Per- and Polyfluoroalkyl Substances on Service Members

Mark Purdue, Ph.D., National Cancer Institute

Topic Area: Pediatric, Adolescent, and Young Adult Cancers (Testicular Cancer) | Award Mechanism: FY18 Idea Award with Special Focus

Testicular cancer is the most common malignancy in men aged 20 to 40 years old and the most diagnosed cancer in U.S active-duty Servicemen.[1] Of the approximate one in 270 men who will develop testicular cancer annually, a further 400 will die this year.[2] Man-made compounds known as per- and polyfluoroalkyl substances, or PFAS, have been associated with the formation of cancer-causing testicular germ cells tumors. PFAS such as perfluorooctanoic acid, or PFOA, were previously used in firefighting foams at military installations, resulting in water contamination. PFOA has thus far been the only PFAS examined with links to testicular cancer; however, those studies were limited to small sample sizes and indirect exposure.

Funded by an FY18 Peer Reviewed Cancer Research Program Idea Award with Special Focus, Purdue and his research team sought to better clarify the causative link between 12 PFAS and testicular cancer among U.S. Air Force Servicemen. Researchers performed a case-control analysis investigating the associations between testicular germ cells tumors risk and prediagnostic concentration of PFAS in blood serum. The study utilized prediagnostic serum samples from the Department of Defense Serum Repository, which contained samples from Air Force Servicemen, 500 of whom developed testicular cancer and 500 cancer-free controls. Investigators found no evidence of an association with testicular germ cells tumors for serum concentrations of PFOA or several other PFAS. Novel evidence, however, found an elevated risk of testicular germ cells tumors with exposure to perfluorooctane sulfonate, or PFOS, another type of PFAS. The data indicated that members of the military exposed to PFOS were most likely to develop testicular cancer later in life. Additional studies are needed to confirm this finding in Service Members.

Purdue's team examined potential predictors of serum PFAS concentrations among Servicemen to better understand patterns of exposure in the Air Force. Through statistical analysis of PFAS serum concentrations it was determined that U.S. Air Force Servicemen stationed at installations which used PFAS-containing firefighting foams generated higher serum levels of PFAS. Further statistical analysis showed an increased risk of testicular germ cells tumors for pilots and Servicemen with aircraft maintenance jobs. This may suggest Service Members with specific roles should be screened sooner due to greater risk for testicular cancer.

This study was the first to conduct direct serum assessments of PFAS exposure in connection to testicular cancer with U.S. Servicemen. Based on these results, Purdue applied and was awarded an Investigator-Initiated Research Award – Human Subjects through CDMRP's Toxic Exposures Research Program, to further interrogate military service-related predictors of elevated PFAS serum concentrations and their associations with testicular germ cells tumors risk. This important research could lead to evidence-based changes to regulation of PFAS in military uses and inform the development of PFAS contamination and exposure guidelines for both military and civilian populations.

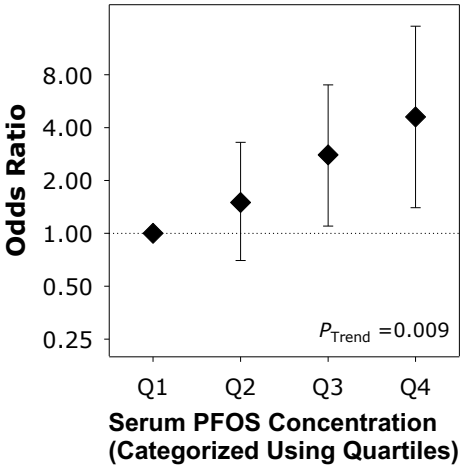


Figure 4: *Association between PFOS concentration (categorized using quartiles as cutpoints) in banked sera collected after several years (median 5.8 years) of military service and risk of testicular cancer in Air Force Service Members.*

Figures Provided by the Principal Investigator

References:

[1] L.A. Lovejoy et al. "Cancer Incidence and Etiology in the Active Duty Population of U.S. Military," *Military Medicine* 189, no. 1-2 (2021). https://doi.org/10.1093/ milmed/usac297

[2] Johns Hopkins Medicine. 2019, November 19. Testicular Cancer Statistics. https://www.hopkinsmedicine.org/health/conditions-and-diseases/testicular-cancer/testicular-cancer-statistics

Photoregulated CAR T-Cells for Precision Immunotherapy and Enhanced Safety

Gang Han, Ph.D., University of Massachusetts Medical School

Topic Area: Immunotherapy | Award Mechanism: FY18 Idea Award with Special Focus

In the last decade, chimeric antigen receptor, or CAR T-cell, therapies have successfully treated some blood cancers. CAR-T cells are made by collecting immune cells called T cells from a patient's blood and engineered to express the CAR, which specifically recognizes and targets a protein on the surface of cancer cells.[1] Currently, there is no system in place to control activation and deactivation of CAR-T cells once administered to a patient. In some cases, dysregulated CAR T-cells can result in systemic inflammatory responses called cytokine release syndrome, resulting in organ damage. There is a need to address these concerns of CAR T-cell therapy to better serve these patient populations and mitigate unwanted side effects.

Han sought to control CAR T-cell activation through adding a light-responsive nanotechnology component to current CAR-T cells that target CD19, a protein with increased expression in blood cancers. This would enable the CAR-T cells to be activated and deactivated via light wave signaling. Han and his team developed light-activated CAR-T cells by testing a series of photo or light receptors to find optimized cell function. The selected light-activated CAR-T cells also showed great ability to participate in photoactivation and destroy CD19 expressing tumor cells upon activation, demonstrating a 30% increase in culture tumor cell death compared to current CAR T-cell models.

Han and his team also devised new lanthanide-doped up-conversion nanoparticles, or UCNPs, to be combined with the light-activated CAR T-cell model. UCNPs convert energy from light to facilitate penetration through tissues, allowing for light-activated CAR-T cells to be activated and function in an optimal state. To determine biological system safety, the UCNPs were tested in a mouse population, resulting in no significant increase in immune cell levels, inflammation or organ damage.

To evaluate the compatibility of the UCNP-conjugated light-activated CAR T-cell model in biological systems, Han and his team performed further experiments in a mouse model. Results demonstrate that the UCNP-conjugated light-activated CAR T-cell model lead to reduced tumor growth. Additionally, the UCNP-conjugated light-activated CAR-T cells mitigated the side effects seen in conventional CAR-T cells, including cytokine release syndrome.

Han and his team found that light-activated CAR-T cells can provide safe and accurate cancer treatment, permitting activation and deactivation on command and the ability to be location-specific in that activation. This specificity minimizes the risks of CAR T-cell treatment. The study's results suggest a potential that CAR T-cell therapy can be personalized for patient needs in timing, location and dosage of treatment.

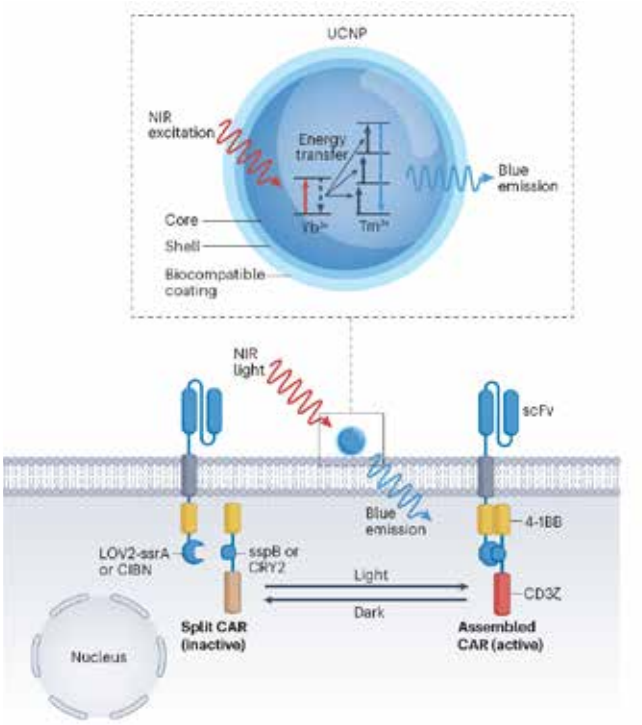


Figure 5: *Diagram showcases a photo-regulated CAR-T system with UCNPs, offering precise spatiotemporal control for cancer immunotherapy. UCNPs convert near-infrared light into blue light, activating split CAR components to assemble into functional CARs only at targeted sites. This innovative system minimizes off-target effects, reduces toxicity and enhances the safety and precision of CAR-T therapy.*

Figures Provided by the Principal Investigator

Reference:

[1] National Cancer Institute. CAR T Cells: Engineering Patients' Immune Cells to Treat Their Cancers. Accessed October 17, 2023. https://www.cancer.gov/about-cancer/treatment/research/car-t-cells

Publication:

N. T. Nguyen et al. "Nano-Optogenetic Engineering of CAR T Cells for Precision Immunotherapy with Enhanced Safety," *Nature Nanotechnology* 16, no. 12 (2021):1424-1434. https://doi.org/10.1038/s41565-021-00982-5

Targeted Gold Nanoparticles (AuNPs) for Potent Alpha-Particle Radiotherapy of Brain Cancer

Yang Liu, Ph.D., Duke University

Topic Area: Brain Cancer | Award Mechanism: FY18 Horizon Award

Glioblastoma Multiforme, or GBM, is an aggressive primary brain cancer with a low life expectancy.[1] More than 10,000 individuals are newly diagnosed with GBM annually in the United States[2], to include Service Members and Veterans who may be at higher risk due to exposure to ionizing radiation and workplace carcinogens.[3] The introduction of targeted alpha-particle therapy in cancer treatment has shown the potential in exceeding the current standard-of-care treatment for tumors like GBM. This therapy employs radioactive elements known as alpha particles to eliminate nearby cancer cells by damaging their DNA, thereby hindering their proliferation. These alpha particles are tethered to a delivery agent or carrier molecule, ensuring that the radiation specifically targets the tumor cells. Unfortunately, current delivery agents have drawbacks that limit their clinical application, resulting in suboptimal outcomes. Because of this, a new delivery system is needed that effectively targets the right cells without allowing the radiolabel to dissociate from the therapeutic agent.

Liu received an FY18 Horizon Award focused on enhancing delivery platforms for alpha-particle radiotherapy for brain cancer. To achieve this, the research team synthesized star-shaped gold nanoparticles and combined them with a radioactive molecule called astatine-211 and small peptides. This approach resulted in a radiotherapy delivery system that selectively targets brain tumors while avoiding the limitations of current treatment methods. The gold nanoparticles were first synthesized and evaluated for bonding potential. To be effective and safe, the gold nanoparticles must be small enough to clear the body through the renal system and large enough to be conjugated with the therapeutic astatine-211 particle and brain-targeting peptides. Liu and his team assessed the strength of the chemical bond between the gold nanoparticles and astatine-211 and found that it was strong enough to prevent dissociation. The team also tested peptides c(RGDfK) and angiopep-2, both targeting GBM, to determine which was most effective for treating the brain.

Particle dissociation and off-target effects are typical limitations of current delivery systems. Consequently, they assessed the stability of the new gold nanoparticles delivery platform by measuring the amount of free astatine-211 in mouse serum after incubation. They observed that, after 24 hours, 99.6% of astatine-211 remained attached to the gold nanoparticles, providing data that astatine-211 did not dissociate. To understand the uptake and distribution of the gold nanoparticles within the body's tissues, mice received one dose of the gold nanoparticles intravenously, and organs were evaluated for free astatine-211 levels at varying time points. The team found that organs of interest showed high levels of the gold nanoparticles and a low degree of dissociation, indicating that the gold nanoparticles could provide cell selectivity and deliver astatine-211 to tumor cells effectively.

Next, the researchers evaluated the therapeutic potential of the astatine-211-labeled gold nanoparticles by monitoring tumor growth after continuous injection of either astatine-211-labeled gold nanoparticles or placebo treatment in mice with human glioma tumors. Results demonstrated that the average tumor volume in the placebo group increased seven times more than in the treatment group, indicating that astatine-211-labeled gold nanoparticles have the potential to inhibit tumor growth.

Overall, Liu and his team successfully synthesized gold nanoparticles with the potential to enhance radiotherapy for GBM. The animal studies revealed encouraging outcomes, as these nanoparticles selectively accumulated in the brain, impeding tumor growth while minimizing astatine-211dissociation. He hopes to further evaluate astatine-211-labeled gold nanoparticles' capabilities through future preclinical and clinical studies. Given the limited immunotherapy options for GBM patients, this discovery could benefit future cancer patients by providing therapeutic treatment with improved efficacy and fewer side effects.

References:

[1] M.E. Davis. "Glioblastoma: Overview of Disease and Treatment," *Clinical Journal of Oncology Nursing* 20, no. 5 (2021):S2-S8. https://doi.org/10.1188/16.CJON.S1.2-8

[2] Quinn T. Ostrom et al., "CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2016—2020," *Neuro-Oncology* 25, no. 12 supplement 2 (2023):iv1-iv99. https://doi.org/10.1093/neuonc/noad149

[3] John R. Bihn et al., "Brain Tumors in United States Military Veterans," *Neuro-Oncology* 26, no. 2 (2024): 387-96. https://doi.org/10.1093/neuonc/ noad182

Publication:

Y. Liu et al. "Gold Nanostars: A Novel Platform for Developing 211At-Labeled Agents for Targeted Alpha-Particle Therapy," *International Journal of Nanomedicine* 16 (2021):7297-7305. https://doi.org/10.2147/IJN.S327577

Novel Circulating Biomarker for Hepatocellular Carcinoma

Ju Dong Yang, M.D., Cedars-Sinai Medical Center

Topic Area: Liver Cancer | Award Mechanism: FY19 Career Development Award

Hepatocellular carcinoma, or HCC, is the most common liver cancer and one of the deadliest. Despite the considerable burden that HCC causes in the United States, there remains a need for more effective and accurate diagnostic tools for monitoring treatment response and disease progression.[1] Circulating tumor cells, or CTCs, are a novel and promising biomarker in the cancer research field. They can be isolated from the patient's blood, providing a noninvasive alternative to traditional tissue biopsies. Yang and his team hypothesized that classifying HCC CTCs based on their unique gene expression profiles will augment their utility for predicting cancer prognosis and, thus, have developed a highly sensitive tool for detecting liver circulating tumor cells.

Yang received an FY19 Career Development Award to test the prognostic potential of their novel HCC circulating tumor cells scoring system. The scoring system is a two-step approach that allows selective isolation and characterization of HCC circulating tumor cells. Specifically, the system uses a NanoVelcro circulating tumor cells assay to isolate HCC circulating tumor cells from blood samples, then quantifies mRNA expression in these circulating tumor cells using the NanoString nCounter platform. In parallel, the team uses an integrated data analysis framework to develop a prognostic mRNA panel called the HCC CTC Risk Score panel. In previous work, the team identified 10 genes highly expressed in HCC with promising prognostic value. After confirming the accuracy of the HCC CTC risk score in cell lines and artificial blood samples, Yang utilized his FY19 Career Development Award to test the predictive capacity of the scoring system by using blood samples from 40 HCC patients and six healthy individuals.

The team successfully isolated circulating tumor cells from 92.5% of HCC patients, and the HCC CTC risk score demonstrated excellent accuracy in discriminating between HCC patients and healthy controls. Additionally, there was a clear distinction of results between the high-risk and the low-risk HCC groups, with the high-risk group having a significantly worse prognosis, as reported by the HCC CTC risk score. These findings confirm that the HCC CTC risk score effectively identifies HCC patients and can predict disease prognosis. Although more work is needed to confirm the applicability of the HCC CTC risk score, this novel screening tool holds promise for rapid translation. It could revolutionize patient care by providing a noninvasive method to determine disease prognosis. Ultimately, this technology could lead to more personalized treatment strategies, thereby improving patients' quality of life.

Reference:

[1] Romain Donne and Amaia Lujambio "The Liver Cancer Immune Microenvironment: Therapeutic Implications for Hepatocellular Carcinoma," *Hepatology* 77, no. 5 (2023): 1773- 96, https://doi.org/10.1002/hep.32740

Publication:

Y. T. Lee et al. "Circulating Tumor Cell-Based Messenger RNA Scoring System for Prognostication of Hepatocellular Carcinoma: Translating Tissue-Based Messenger RNA Profiling Into a Noninvasive Setting," *Liver Transpl* 28, no. 2 (2022):200-214. doi: 10.1002/lt.26337

Preclinical Testing of Novel Immunotherapies for the Treatment of Neuroblastoma

Rosa Nguyen, M.D., Ph.D., National Cancer Institute

Topic Area: Neuroblastoma | Award Mechanism: FY19 Horizon Award

Neuroblastoma is a cancer that affects developing nerve cells and is most common in children, especially those under the age of five.[1] Neuroblastomas account for 6%-10% of childhood cancers[2], with 800 new cases diagnosed each year in the United States.[3] Immunotherapy has emerged as a promising approach for treating various cancer, including neuroblastoma. This innovative strategy harnesses the power of the immune system to combat cancer. Specifically, tumor-targeting antibodies selectively label cancer cells, thereby targeting them for destruction by the immune system. Antibodies against disialoganglioside, or GD2, a protein on the surface of neuroblastoma cells, is part of standard care for patients with high-risk neuroblastoma. However, 50% of patients receiving this treatment do not achieve long-term remission. These statistics underscore the urgent need to improve patient outcomes and emphasizes the importance of investigating new therapeutic strategies.

Nguyen received an FY19 Horizon Award to improve immunotherapy by developing and testing novel immunocytokines in preclinical models of neuroblastoma. Immunocytokines combine an antibody with a cytokine, a secreted molecule that impacts cell behavior, including that of immune cells. Combining a cytokine with an antibody against neuroblastoma allows for targeted recruitment of immune cells to the tumor. Previously, GD2 antibody, or anti-GD2, was combined with a cytokine called IL2 to form an immunocytokines called aGD2-IL-2. Studies showed that aGD2-IL-2 was only effective in patients previously treated with other therapies who had little evidence of cancer and was ineffective against larger, bulky tumors.

Consequently, Nguyen's research team synthesized two novel immunocytokines, aGD2-IL-15 and aGD2-IL-21, using cytokines IL15 and IL21. To assess the performance of these immunocytokines, the team compared the antitumor activity of their novel immunocytokines candidates to existing immunocytokines, aGD2-IL-2, using mouse models of neuroblastoma. Therapy with aGD2-IL-2 is known to work in part by regulating the activity of natural killer, or NK, immune cells, which act by directly killing tumor cells. When tested in mice with a modified immune system that relied mostly on NK cells, all immunocytokines performed similarly. However, when tested in mice with a fully functioning immune system, the novel ICs, aGD2-IL-15 and aGD2-IL-21, exerted greater effects than the existing immunocytokines, aGD2-IL-2, as evidenced by reduced tumor size and greater long-term survival. These results indicated that immune cells beside NK cells must be playing a role in the efficacy of the novel ICs, aGD2-IL-15 and aGD2-IL-21.

The team then sought to understand how these treatments impact the immune system. They determined that treatment with aGD2-IL-15 and aGD2-IL-21 not only increased NK cell activity, but also recruited additional immune cells involved in promoting tumor cell death. Increasing antitumor activity in combination with decreasing immune suppression results in the improved outcomes seen in mouse models with aGD2-IL-15 and aGD2-IL-21 treatment. Collectively, these studies illustrate that these novel immunocytokines have significant effects on neuroblastoma tumors in preclinical models and may translate well to clinical use, potentially providing additional treatment options to patients who do not respond well to current therapies.

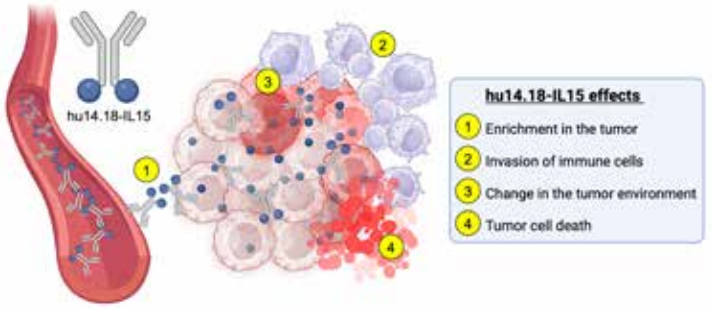


Figure 6: *Mechanisms by which hu14.18-IL15 enhances ADCC in the tumor microenvironment (TME). After enrichment in the TME (1), other immune cells are attracted and invade the tumor (2). IL-15 remodels the cellular subsets like tumor-associated macrophages. Altogether, these changes lead to neuroblastoma cell death.*

Figures Provided by the Principal Investigator

References:

[1] St. Jude Children's Research Hospital. Neuroblastoma Treatment. Accessed March 21, 2023, https://www.stjude.org/disease/neuroblastoma.html

[2] C.A. Stiller and D.M. Parkin, "International Variations in the Incidence of Neuroblastoma," *International Journal of Cancer* 52, no. 4 (1992): 538-543. https://doi.org/10.1002/IJC.2910520407

[3] American Cancer Society. About Neuroblastoma. Accessed March 26, 2025, https://www.cancer.org/cancer/types/neuroblastoma/about/key-statistics.html

Publication:

R. Nguyen et al. "Anti-GD2 Antibodies Conjugated to IL15 and IL21 Mediate Potent Antitumor Cytotoxicity Against Neuroblastoma," *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research* 28, no. 17 (2022):3785-3796. https://doi.org/10.1158/1078-0432.CCR-22-0717

Nonendoscopic Screening to Impact Esophageal Cancer in Veterans

Katarina Greer, M.D., Cleveland VA Medical Research and Education Foundation

Topic Area: Esophageal Cancer | Award Mechanism: FY20 Impact Award – Clinical Trial

Each year, over 22,000 individuals in the United States will be diagnosed with esophageal cancer and over 16,000 succumb to the disease.[1] Among those at risk for esophageal cancer are U.S. Service Members who experience increased occupational exposures to carcinogenic agents, including ionizing radiation, a known risk factor for esophageal cancer.[2] Most patients are diagnosed at a late stage when the prognosis is poor. Early detection of esophageal adenocarcinoma and its precursor lesion, Barrett's esophagus, or BE, has the potential to improve survival these cancer patients.[3,4] Greer received an FY20 Impact Award – Clinical Trial to improve early detection and diagnosis of cancerous and precancerous esophageal cancer.

The study's primary objective is to revolutionize the detection and diagnosis of BE and esophageal adenocarcinoma by introducing a non-endoscopic detection method suitable for primary care settings. To achieve this, the researchers evaluated the diagnostic accuracy, tolerance and acceptability of EsoCheck a non-endoscopic esophageal balloon sampling device, coupled with EsoGuard, a DNA-based screening assay. Veterans at Louis Stokes Cleveland Veteran Affairs Medical Center who met the American College of Gastroenterology Guideline screening criteria for BE, underwent EsoCheck coupled with EsoGuard as well as the gold standard for diagnosis, sedated endoscopy. Among the 124 participants who completed both tests, EsoCheck and EsoGuard exhibited high sensitivity (92.9%) and negative predictive value (98.6%).[5] Although anxiety levels among study participants were notable, the overall tolerance and acceptability of EsoCheck sampling were relatively high.

With these promising results, Greer applied for and received an FY23 PRCRP Impact Award – Clinical Trial, "Nonendoscopic Screening for Barrett's Esophagus and Esophageal Cancer in At-Risk Veterans Without History of Chronic Gastroesophageal Reflux," to validate the application of EsoCheck and EsoGuard screening to a broader group of individuals. BE is associated with incidence of gastroesophageal reflux disease, or GERD, commonly referred to as "heartburn." While BE is the only known precursor lesion for ophageal adenocarcinoma, 40% of those diagnosed with esophageal cancer report no prior history of GERD symptoms. Greer will perform a pilot clinical trial to determine if applying the EsoCheck and EsoGuard technology to screen at-risk subjects who have not experienced symptoms of GERD can increase early detection of BE.

Greer's current findings suggest that EsoGuard holds promise as a screening tool for BE and esophageal adenocarcinoma, boasting high sensitivity and negative predictive value and the potential to be more widely available and tolerated than sedated endoscopy. The results of both of Greer's funded studies could potentially reduce morbidity and mortality from esophageal cancer through early diagnosis.

References:

[1] American Cancer Society. Esophagus Cancer. Accessed September 27, 2024. https://www.cancer.org/cancer/types/esophagus-cancer/about/key-statistics.html

[2] International Agency for Research on Cancer Working Group on the Evaluation of Carcinogenic Risks to Humans. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*: A Review of Human Carcinogens, Part D: Radiation, Volume 100D (2012), World Health Organization Press, https://publications.iarc.fr/121

[3] E.O. Then et al. "Esophageal Cancer: An Updated Surveillance Epidemiology and End Results Database Analysis," *World J Oncol* 11, no. 2 (2020):55-64. https//doi. org/10.14740/wjon1254.

[4] N.J. Shaheen et al. "American College of Gastroenterology. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus," *Am J Gastroenterol* 111, no. 1 (2020):30-50.

[5] Biospace. Lucid Diagnostics Announces Positive Data from the First Prospective Clinical Validation Study of EsoGuard® Esophageal Precancer Testing in a Screening Population. Accessed September 27, 2024. https://www.biospace.com/lucid-diagnostics-announces-positive-data-from-the-first-prospective-clinical-validation-study-of-esoguard-esophageal-precancer-testing-in-a-screening-population?s=110

Publication:

K.B. Greer et al. "Nonendoscopic Screening for Barrett's Esophagus and Esophageal Adenocarcinoma in At-Risk Veterans," *Am J Gastroenterol*., ahead of print, July 2024. https.//doi.org/10.14309/ajg.0000000000002962

Detection of Early Relapse Using Circulating miR371a-3p in Patients with Early-Stage Testicular Germ Cell Tumors

Lucia Nappi, M.D., Ph.D., The University of British Columbia

Topic Area: Germ Cell Cancer | Award Mechanism: FY21 Career Development Award

Testicular cancer, a type of germ cell tumor, is the most frequent tumor arising in young men, a population prominently represented in Service Members. Depending on tumor type and risk factors, 15%-50% of patients will experience a relapse; therefore, testicular cancer patients must undergo monitoring for years after their initial treatment.[1] This post-treatment surveillance can include up to six rounds of computed tomography, or CT, just in the first post-treatment year, yet CT cannot reliably detect very small tumor volumes and exposes patients to radiation that can increase secondary cancer risk.[2,3] Nappi received an FY21 Career Development Award to develop a nonradiological technique to identify testicular patients at risk for relapse and reduce the burden of post-treatment surveillance.

Nappi identified miRNA-371, a small non-coding RNA specific for germ cell tumors, as a potential biomarker to detect the disease at low or very low tumor volumes. Preliminary work by the principal investigator showed mRNA-371 had the potential to be more accurate than surveillance using CT. To further unravel the potential of this miRNA, Nappi proposed to study patients who had undergone removal of a testicle for their primary disease and had been determined to have no evidence of disease. The team analyzed blood samples of 101 patients diagnosed with early-stage testicular cancer and identified 22 patients positive for miRNA-371 expression. During the study period, 35 patients, including all 22 patients with positive miRNA-371 expression, had confirmed tumor relapse. In addition, in eight of the 22 patients, miRNA-371 expression was positive before the tumor relapse became clinically evident. All 66 patients who did not relapse were confirmed to be miRNA-371 negative.

The results of these analyses supported initiation of a phase 2 clinical trial (MAGESTIC Trial: MiRNA in Detecting Active Germ Cell Tumors in Early Suspected and MetastaTIC Disease Trial, NCT060608730).[4] The trial, which is not funded by this award, will measure expression of miR371 via blood draws in testicular cancer patients who have had their primary tumor excised. Patients with elevated miR371 will be recommended for surgery to resect retroperitoneal lymph nodes, nearby lymph nodes which are the first site for testicular cancer spread.

Nappi's ongoing work on her PRCRP-funded project will include investigating two methodologies (real time polymerase chain reaction and nucleic acid sequence-based amplification) to determine which is the most accurate at identifying very small amounts of miRNA-871 in the blood. Determining the clinical significance of mi-RNA371 as a less invasive, more accurate detection method could potentially reduce the utilization of toxic and invasive treatments and avoid long-term impacts on the lives of young patients.

References:

[1] S. Fischer et al. "Outcome of Men With Relapses After Adjuvant Bleomycin, Etoposide, and Cisplatin for Clinical Stage I Nonseminoma," *Journal of Clinical Oncology* 38, no. 12 (2019):1322-1331.

[2] P.U. Dalal. "Imaging of Testicular Germ Cell Tumours," *Cancer Imaging* 6, no. 1 (2006):124-134.

[3] C.-F. Cao et al. "CT Scans and Cancer Risks: A Systematic Review and Dose-Response Meta-Analysis," *BMC Cancer* 22 (2022):1238.

[4] National Cancer Institute. 2023. Phase II Trial of Serum Micro RNA-371 in Detecting Active Germ Cell Tumors in Patients with Suspected Regional Disease - (MAGESTIC Trial: MiRNA in Detecting Active Germ Cell Tumors in Early Suspected and MetastaTIC Disease Trial).

Publications:

L. Nappi et al. "Long Term Follow-Up Analysis of Plasma miR371 Expression to Detect Early Relapse in Patients With Clinical Stage I Testicular Germ Cell Tumors on Surveillance," *J Clin Oncol* 41, suppl. 16 (2023) abstr. 5006. Oral abstract presentation at the 2023 ASCO annual meeting 2023 – Chicago, June 4, 2023.

CONSUMER ADVOCATE HIGHLIGHTS

Julie Krause: Battling Oligometastatic Colorectal Cancer

Julie Krause, Fight Colorectal Cancer

During a routine colonoscopy in 2010, Julie Krause's doctors discovered a three-millimeter polyp, or abnormal tissue growth, and diagnosed her with colon cancer. Surgery was optional, but Krause decided to have a section of her colon removed as part of treatment. Following further tests, physicians discovered that one of her lymph nodes was positive for cancer, leading to a diagnosis of stage III colon cancer.

Doctors gave Krause a promising prognosis: they said with chemotherapy, she had a 95% chance of beating the cancer. Twelve rounds of chemotherapy left Krause with nerve damage that created pain and numbness.[1] Despite the side effects, she believed more chemotherapy was the best treatment and pushed through.

Doctors continued to track Krause's progress by monitoring the levels of carcinoembryonic antigen, or CEA, a protein that can indicate the presence of cancer when found at higher-than-normal levels. Krause's CEA levels were rising at the end of 2011, and a CT scan in early 2012 revealed that the cancer spread to her liver. Krause underwent another surgery to remove the liver tumor; however, her CEA levels continued to increase. Six weeks post-surgery, when a second CT scan revealed that the cancer had spread to two additional sites, Krause underwent another round of chemotherapy to combat the disease.

Near the end of 2012, doctors told Krause that there was no evidence of disease, but she would likely need chemotherapy for the rest of her life, which was only expected to be three years. Krause has outlived that prediction, but in the subsequent years experienced additional liver metastases, lung metastases and endured three more surgeries, multiple rounds of chemotherapy and radiofrequency ablation, a method of killing cancer cells via electrical energy and heat.

Krause acts as an advisor to the Alliance for Clinical Trials and an advocate with Fight CRC, the organization she represents as a peer review panel member for the PRCRP. She has also acted as a mentor to new panel consumer advocate reviewers for the PRCRP. Krause states, "I found [acting as a mentor] rewarding, passing my knowledge of peer review and research resources to new patient advocates."

While Krause finds her role as a consumer advocate to be challenging, she sees it as an opportunity to play a part in finding a cure for cancer and giving back to the community that supported her during her own cancer journey. She said that being a consumer advocate has "given me a reason to push forward, not giving cancer the opportunity to ruin my life; pushed me to new challenges; taken me out of my comfort zone; and allowed me to make some wonderful new friendships. I love it!"

Reference:

[1] Mayo Clinic. Peripheral Neuropathy. 2023. https://www.mayoclinic.org/diseases-conditions/peripheral-neuropathy/symptoms-causes/syc-20352061

Karen Sachse: Empowered by Experience in Bladder Cancer Care

Karen Sachse, R.N., M.S.N., CNS-BC, Bladder Cancer Advocacy Network

Bladder cancer symptoms often mimic those of urinary tract infections, such as painful and urgent urination or blood in the urine. Two years prior to her bladder cancer diagnosis, Karen Sachse began experiencing frequent urinary tract infections. She was referred to a urologist who prescribed low-dose antibiotics and cranberry supplements. Sachse soon began experiencing monthly spotting she believed to be a result of her menopausal status and didn't give it much thought. When the frequency of spotting increased to weekly, Sachse's provider assessed her for gynecological issues. The assessment did not identify any gynecological anomalies, but they found a tumor in her bladder.

Surgeons removed a 9x7 centimeter tumor from Sachse's bladder in December 2011. The initial pathology results revealed the that she had low-grade bladder cancer, meaning it was less likely to grow and spread. Her postsurgical treatment regimen involved two rounds of immunotherapy to eliminate any residual cancer. Unfortunately, this treatment regimen was ineffective at eradicating her cancer and, seven months later, she was still positive for disease. She sought a second opinion and was subsequently diagnosed with high-grade bladder cancer. After nine rounds of chemotherapy, Sachse was finally cancer-free.

In the years that followed, Sachse experienced three recurrences, two in 2012 and one in 2014, each requiring one dose of the chemotherapy. In addition to her own battle with cancer, she soon faced the hardship of having a loved one diagnosed with the disease. In 2016, her husband was also diagnosed with bladder cancer. She was by his side through chemotherapy and surgery. Four months later, physicians discovered that the cancer spread to his central nervous system and, sadly, just fifteen months after the initial diagnosis, he passed away.

For the last decade, Sachse has been a dedicated patient advocate for the Bladder Cancer Advocacy Network, or BCAN. Her contributions include working with industry partners to review educational material, participating on the advisory panel for a Patient-Centered Outcomes Research Institute study, serving as part of a survivorship task force and being appointed to the Board of Directors in 2023.

With Sachse's passion for raising bladder cancer awareness and providing support and education to patients and caregivers, BCAN recommended her to the PRCRP to participate at peer review. Of her experience working with the PRCRP, Karen states, "I have always felt that the scientists and medical providers on the panels have given me the opportunity to contribute and have valued my input. The patient voice is essential to the work of the PRCRP!"

Kate Bernstein

Kate Bernstein, St. Baldrick's Foundation

At just 15 months old, Kate Bernstein's younger child became a terrifying statistic: one of the approximately 800 children each year diagnosed with neuroblastoma. The average age of children at diagnosis is about one to two years. Nine out of 10 neuroblastomas are diagnosed by age five. Early signs of neuroblastoma include common symptoms for minor illnesses and even teething, such as irritability, fever, reduced appetite or fatigue.

Bernstein's daughter had mild on-and-off again fevers for about a week when her condition suddenly worsened, with labored breathing. She rushed her daughter to the pediatrician, who diagnosed her child with pneumonia, sending her to the hospital for IV antibiotics. When X-rays failed to show the expected treatment results, doctors ordered a CT scan. Bernstein said her heart sank when she was asked to leave her daughter's bedside for a consultation with the doctor and a social worker about the CT results.

"The farther we got from her room the more I was sure they had found something terrible," Bernstein said. The diagnosis was stage IV high-risk neuroblastoma with MYCN amplification, which meant that the cancer would be more likely to spread in her daughter's system and less likely to respond to treatment.

"By the time we knew what exactly to call [her disease] a few days later, our child already had surgery to implant a giant catheter in her chest and biopsy the tumor that nearly filled the left side of her abdomen," Bernstein said. "We filled pages with notes, asking what felt like an endless list of questions."

The fight for her daughter's life was like a roller coaster of front-line treatment, Bernstein said. She and her family spent weeks in the hospital and worked together to care for their older children.

"Those days would mean little sleep, trying to work while caring for a sick, unhappy kid, and learning what we needed to feel like we had any handle at all on what was going on around us." Her daughter relapsed one week from the end of expected treatment, then again a few months later, just weeks after scans declared she had "no evidence of disease," Bernstein said.

Because of these early relapses, Bernstein's daughter remained in treatment for the next seven years. Most of the treatments she received were therapies that were only studied and designed for use in adults, a common issue with childhood cancers which can be very different from adult-onset cancers. In addition, due to the rapid changes that are occurring during growth, these treatments can have more severe and long-term effects in children. Bernstein's daughter was no exception.

"For our survivor, treatment left her with myriad issues: moderate to profound hearing loss, a collapsed bone that required two surgeries and resulted in a leg-length discrepancy, significant lymphedema that requires custom pressure garments that cost thousands of dollars each and must be worn 23 hours each day, and the need to consult with multiple specialists to oversee the many life-long side effects and likely systemic issues," Bernstein said.

Bernstein became a neuroblastoma consumer advocate with St. Baldrick's Foundation as "a way to give back to those that have helped us and pay forward the incredible kindnesses we've known throughout our daughter's life."

Of her experience reviewing for the PRCRP Bernstein said, "I've seen first-hand how important consumer reviewers are in the process. I've been able to discuss what more-effective, less-toxic treatments for neuroblastoma can mean for patients and families in terms of physical, emotional and financial impacts."

Bernstein said that, while her daughter is thriving today, she worked hard to do so. "More than 11 years after her diagnosis, our daughter is thriving, despite a continued above-average number of medical appointments. She plays two instruments in her school's music program, participates on a swim team and excels in school. But she worked hard for every piece of that normalcy, and so have we. Recently, we celebrated another milestone in our daughter's life that we once thought she may never reach: she became a bat mitzvah. That kind of event is why advocacy and participation in PRCRP programs is so important to us."

PRCRP CLINICAL PIPELINE

CURRENT PI NAME (CURRENT PERFORMING ORG)	THERAPY OR TECHNIQUE	STUDY DESCRIPTION	PHASES
ALL TOPIC AREAS			
Yennu, Sriram (M.D. Anderson Cancer Center, University of Texas)	Psychoeducation Intervention	This study aims to determine if combination therapy of psychoeducation plus open-label placebo will result in improvement of cancer-related fatigue using a randomized controlled trial.	Phase 0/Pilot
BLADDER CANCER			
Siddiqui, Mohummad (University of Maryland, Baltimore); Putluri, Nagireddy (Baylor College of Medicine); McConkey, David (Johns Hopkins University)	Magnetic Resonance Imaging	The project will examine the potential of hyperpolarized 13C metabolic MRI to stage,risk-stratify and monitor treatment response of muscle-invasive bladder cancer.	Phase 0/Pilot
Poch, Michael (H. Lee Moffitt Cancer Center and Research Institute at University of South Florida); Rejniak, Katarzyna (H. Lee Moffitt Cancer Center and Research Institute at University of South Florida); Pilon-Thomas, Shari (H. Lee Moffitt Cancer Center and Research Institute at University of South Florida)	Adoptive Cell Therapy	The study evaluates the feasibility, safety and tolerability of intravesical adoptive cell therapy using TIL (tumor infiltrating lymphocytes) in participants with urothelial cell carcinoma (UCC) non-muscle invasive bladder cancer (NMIBC).	Phase 1
BLOOD CANCER			
Pemmaraju, Naveen (M.D. Anderson Cancer Center, University of Texas); Lane, Andrew (Dana-Farber Cancer Institute); Abdel-Wahab, Omar (Sloan Kettering Institute for Cancer Research)	Combination Antineoplastic Agents	This trial combines azacitidine, tagraxofusp and venetoclax in patients with Blastic plasmacytoid dendritic cell neoplasm, an aggressive type of blood and bone marrow cancer, that is untreated, has relapsed or does not respond to treatment (refractory).	Phase 1
Fruman, David (University of California, Irvine)	Combination Statin Drug and Chemotherapeutic	The PI is conducting a dose-escalation, open-label clinical trial determining the safety and tolerability of adding Pitavastatin to Venetoclax in subjects with chronic lymphocytic leukemia (CLL) or acute myeloid leukemia (AML).	Phase 1
Pemmaraju, Naveen (M.D. Anderson Cancer Center, University of Texas)	Targeted Antineoplastic Agent	This trial will measure whether patients with acute myeloid leukemia will benefit from treatment with small molecule inhibitor PCLX-001 and determine safe and biologically effective doses. In addition, whether levels of N-myristoyltransferase (NMT), proteins that are associated with several types of blood cancers, are reliable predictors of treatment outcomes.	Phase 1
Borthakur, Gautam (M.D. Anderson Cancer Center, University of Texas)	Monoclonal Antibody	This is a trial of anti-IL1RAP antibody Nadunolimab in patients with myelodysplastic syndrome and acute myelogenous leukemia.	Phase 1/2

CURRENT PI NAME (CURRENT PERFORMING ORG)	THERAPY OR TECHNIQUE	STUDY DESCRIPTION	PHASES
BRAIN CANCER			
Huang, Jianping (University of Florida)	Targeted Immunotherapy	The project includes a dose-escalation trial to evaluate primary clinical endpoints of feasibility and safety, and CNS trafficking of intravenously delivered CD70 CAR T cells in patients with newly diagnosed, CD70+ glioblastoma.	Phase 1
Loughan, Ashlee (Virginia Commonwealth University); Nathanson, David (University of California, Los Angeles); Cloughesy, Timothy (University of California, Los Angeles); Ellingson, Benjamin (University of California, Los Angeles)	Behavioral Intervention	The PI will compare the Managing Cancer and Living Meaningfully (CALM), an empirically supported psychotherapeutic intervention, with treatment as usual in those with malignant brain cancer diagnoses.	Phase 2
BRAIN CANCER AND PAYAC			
Fouladi, Maryam (Research Institute at Nationwide Children's Hospital)	Combination Antineoplastic Agents	The study team aims to determine efficacy of drugs ribociclib and everolimus to treat pediatric and young adult patients newly diagnosed with a high-grade glioma (HGG), including DIPG, that have genetic changes in pathways (cell cycle, PI3K/mTOR) that these drugs target.	Phase 2
BRAIN CANCER AND PEDIATRIC BRAIN TUMORS			
Cassady, Kevin (Research Institute at Nationwide Children's Hospital); Mardis, Elaine (Research Institute at Nationwide Children's Hospital); Markert, James (University of Alabama at Birmingham)	Oncolytic Virus	This study will determine safety and tolerability of C134, an oncolytic virus, when administered twice into the brain where the glioma is located/has been resected.	Phase 1
COLORECTAL CANCER			
Waldman, Scott (Thomas Jefferson University); Weinberg, David (Institute for Cancer Research); Dominitz, Jason (Seattle Institute for Biomedical and Clinical Research)	Combination Immunotherapy and Bacterium	The goal of this study is to optimize/characterize a combination therapy of immune checkpoint blockade and hypoxia-targeting bacterium Lactococuss lactis to reduce toxicity of treatment for colorectal cancer.	Phase 2
Wald, David (Case Western Reserve University); Anthony, Donald (Case Western Reserve University)	Immunotherapy	The goal of this clinical trial is to test the safety and efficacy of Natural Killer (NK) cell immunotherapy for treatment of relapsed/refractory colon cancer.	Phase 1/2
Hubbard, Joleen (Mayo Clinic)	Combination Vaccine and Chemotherapy	The goal of the study is to investigate the safety, tolerability, immunogenicity and efficacy of the PolyPEPI1018 vaccine in combination with TAS-102 in treating patients with colorectal cancer.	Phase 1
Snook, Adam (Thomas Jefferson University); Bashir, Babar (Thomas Jefferson University)	Vaccine	The goal of the study is to target guanylate cyclase 2c transmembrane protein to induce a robust GUCY2c-specific immune response and antitumor efficacy in MRD+ CRC patients by boosting immunization of GUCY2C-directied AD5.F35 + Lm.	Phase 1

CURRENT PI NAME (CURRENT PERFORMING ORG)	THERAPY OR TECHNIQUE	STUDY DESCRIPTION	PHASES
ESOPHAGEAL CANCER			
Adusumilli, Prasad (Sloan Kettering Institute for Cancer Research)	Immunotherapy	This is a phase 1 trial of intraperitoneal mesothelin-targeted CAR T-cell therapy in patients with mesothelin-positive esophagogastric adenocarcinoma with peritoneal carcinomatosis.	Phase 1
HEAD AND NECK CANCER			
Diefenbach, Michael (Feinstein Institute for Medical Research)	Text Message-Based Program	The intervention in this clinical trial is a text message program designed to promote alcohol cessation tailored to head and neck cancer patients in addition to usual-care advice.	Phase 0/ Pilot
Deng, Jie (University of Pennsylvania)	Behavioral Intervention	This trial will evaluate the effectiveness of a standardized lymphedema and fibrosis self-management program (LEF-SMP) to improve LEF self-management and reduce LEF-associated symptom burden, functional deficits and improve quality of life in head and neck cancer survivors.	Phase 0/ Pilot
LIVER CANCER			
Suzuki, Ayako (Duke University); Diehl, Anna Mae (Duke University); Abdelmalek, Manal (Mayo Clinic)	Statin Drug	This single center, double-blind, randomized, placebo-controlled trial will evaluate the efficacy and safety profile of 96-week treatment with atorvastatin in patients with nonalcoholic steatohepatitis, a condition that increases risk of developing liver cancer.	Phase 2
MELANOMA			
Slingluff, Craig (University of Virginia); Isaacs, James (Cleveland Clinic Foundation); Bullock, Timothy (University of Virginia)	Vaccine	This trial studies the effects of an enhanced melanoma vaccine made with 6MHP, NeoAg-mBRAF, polyICLC and CDX-1140 help boost the immune system's response in treating patients with stage IIB-IV melanoma.	Phase 1
NEUROBLASTOMA AND IMMUNOTHERAPY			
Hucks, George (University of North Carolina at Chapel Hill); Savoldo, Barbara (University of North Carolina at Chapel Hill)	Immunotherapy	The trial will assess the safety and efficacy of CAR-T cell therapy in children with relapsed/refractory neuroblastoma and identify laboratory tests that will predict responses and outcomes.	Phase 1
PANCREATIC CANCER			
Li, Xin (New York University); Cohen, Deirdre (Icahn School of Medicine at Mount Sinai); Saxena, Deepak (New York University)	Combination Antibiotics and Immunotherapy	This study is conducting a window of opportunity, multi-institutional, pilot study of antibiotics and pembrolizumab for pre-operative treatment of surgically resectable pancreatic cancer.	Phase 1

CURRENT PI NAME (CURRENT PERFORMING ORG)	THERAPY OR TECHNIQUE	STUDY DESCRIPTION	PHASES
PAYAC			
Chow, Eric (Fred Hutchinson Cancer Center)	Hormone Analog	The proposed study will investigate the feasibility of administering the gonadotropin-releasing hormone analogs (GnRHa) triptorelin for the purposes of fertility preservation as a randomized intervention among newly diagnosed adolescent and young adult cancer patients treated with alkylating agent chemotherapy.	Phase 0/Pilot
Teoh, Deanna (University of Minnesota, Twin Cities)	Behavioral Intervention	This project aims to increase HPV vaccination initiation and completion among adolescent and young adult cancer survivors by implementing a single multilevel intervention focused on the clinic, oncologist and survivor.	Phase 0/Pilot
PEDIATRIC BRAIN TUMORS			
Hwang, Eugene (Children's Research Institute at CNMC)	Combination Therapy	This study will examine the combination of SGT-53, tumor-targeted nanomedicine, with conventional radiation and/or chemotherapy for treatment of pediatric brain tumors.	Phase 0/Pilot
Acharya, Sahaja (Johns Hopkins University)	Radiation	The goal of this trial is to determine whether it is possible to minimize radiation dose to parts of the brain that are important for thinking and learning in children who require radiation to treat their tumor, and if this will help reduce neurocognitive impairments in these patients.	Phase 0/Pilot
THYROID CANCER			
Ferrarotto, Renata (M.D. Anderson Cancer Center, University of Texas)	Immunotherapy	This trial is designed to determine side effects and possible benefits of treatment with monoclonal antibody AL101 before surgery in patients with thyroid cancer.	Phase 1
Laetsch, Theodore (Children's Hospital, Philadelphia); Franco, Aime (Children's Hospital, Philadelphia)	Combination Small Molecule and Radiation Therapy	Patients will undergo a baseline radioactive iodine (RAI) whole body scan (WBS) and another WBS following 28 days of oncogene-specific, targeted therapy to assess if targeting oncogene drivers can improve thyroid cancer response to RAI therapy.	Phase 0/Pilot

PRCRP CLINICAL STUDIES

TOPIC AREA(S)	CURRENT PI NAME (CURRENT PERFORMING ORG)	DESCRIPTION
Liver Cancer	Javle, Milind (M.D. Anderson Cancer Center, University of Texas); Azad, Nilofer (Johns Hopkins University)	This study will leverage samples from clinical trials to identify predictive biomarkers and the mechanisms of acquired resistance for immune checkpoint inhibition in cholangiocarcinoma patients.
Liver Cancer	Duda, Gabriel (Massachusetts General Hospital)	Plasma from hepatocellular carcinoma patients enrolled in a clinical trial will be used to identify potential biomarkers that can improve the therapeutic benefit of radiotherapy for treatment of unresectable liver tumors.
Colorectal Cancer	Dudeja, Vikas (University of Alabama at Birmingham); Roy, Sabita (University of Miami, Coral Gables); Merchant, Nipun (University of Miami, Coral Gables)	The study will evaluate if the gut microbiome composition of metastatic colorectal cancer patients can predict a response to chemotherapy.

TOPIC AREA(S)	CURRENT PI NAME (CURRENT PERFORMING ORG)	DESCRIPTION
Mesothelioma	Lee, Hyun-Sung (Baylor College of Medicine)	This is a prospective clinical observational study to understand the pathogenesis of immunotoxicities that occur in response to immune checkpoint inhibitor therapy.
Germ Cell Cancer	Ketterl, Tyler (Seattle Children's Research Institute); Dieli-Conwright, Christina (Dana-Farber Cancer Institute); Rassekh, Shahrad (University of British Columbia)	The researchers will analyze CT scans from currently open phase 3 randomized control trial to observe if body composition changes during the course of chemotherapy are predictive of the development of toxicity to chemotherapy in malignant germ cell tumors patients.
Blood Cancers	Cairo, Mitchell (New York Medical College); Teachey, David (Children's Hospital, Philadelphia); Hermiston, Michelle (University of California, San Francisco)	Blood, bone marrow, spinal fluid and tumor samples from blood cancer patients enrolled in a clinical trial of bone marrow transplant in combination with immunotherapy will be analyzed to determine why some patients respond to treatment and some do not.
PAYAC and Blood Cancers	Cairo, Mitchell (New York Medical College); Bonifant, Challice (Johns Hopkins University); Lee, Dean (Research Institute at Nationwide Children's Hospital)	Blood collected from pediatric, adolescent and young adult patients with high-risk AML on an ongoing clinical trial of immunotherapies will be analyzed for genomic, immunomic and minimal residual disease characteristics to help inform the next generation of therapeutics.

For more information, please visit
https://cdmrp.health.mil
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