MURTHA CANCER CENTER

DoD Cancer Center of Excellence

MURTHA CANCER CENTER RESEARCH PROGRAM

USU Uniformed Services University

WALTER REED BETHESDA SM

2022 ANNUAL REPORT

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MCCRP MISSION

The mission of the MCC/RP is to improve the diagnosis and multidisciplinary treatment of DoD cancer patients through innovative translational research, evidence-based translational care, and education. Through coordination and alignment with tri-service cancer research initiatives throughout the MHS, the MCC/RP enhances the readiness of the military, its families, and beneficiaries. The MCC/RP employs the unique resources of the DoD leveraged with other federal and civilian partners to research and enhance translational cancer care for SM and DoD beneficiaries.

MCCRP VISION

As the only DoD designated Cancer Center of Excellence MCCRP is the nexus of cancer services and support for the Military Health System with clinical and translational research cancer programs fully integrated with Uniformed Services University, National Cancer Institute, Veterans Administration and other federal and non-federal entities.

Craig D. Shriver, MD, FACS, COL, MC, USA (Ret)
Murtha Cancer Center and Research Program Director

CELEBRATING MURTHA CANCER CENTER DECEMBER 2, 2022

Good morning and thank you all for being here. Thanks to all of the senior leaders both on the dais and in the audience who are in attendance. This is really your Cancer Center and I am humbly privileged to be its caretaker. Fantastic remarks from Colonel Murtha and thank you for your support that has been invaluable for the last decade.

It's amazing to me that we are at this 10th anniversary. It seems like just yesterday that President Woodson and I were in this exact same space at the Founding and Naming Ceremony, but in these short 10 years an incomplete list of accomplishment from your Cancer Center would include the following:

- Hundreds of thousands of patients cared for and given hope
- Accreditation of this Cancer center by 5 different civilian organizations recognizing the highest quality of care, safety, and superior outcomes
- Tens of thousands of patients enrolled in Murtha research studies
- Multiple partnerships forged with Federal and non-Federal entities
- Murtha Cancer Center Research Programs expanded into the 8 Defense Health Agency medical centers and 7 Veteran Health Administration hospitals
- A world-class tissue biorepository totaling over a half a million samples from tens of thousands of patients which have been used in hundreds of research by teams across the nation and the globe
- Unique and paradigm changing research findings published in premier high impact journals, along with the awarding of multiple patents
- Proud growth of our partnerships with National Cancer Institute to include our patient and tissue sharing programs as well as our work together on Federal Cancer Moonshot research leading to the submission of our research data in the NCI Data Commons for open access use by researchers across the globe
- Proud growth of our relationship with the Veterans Health Administration to include our joint Federal Cancer Moonshot studies available to patients in DHA and DHA hospitals
- Being the lead for the Department of Defense in both Cancer Moonshot Initiatives of 2016 and 2022 resulting in the creation of unique and unprecedented research programs such as our proteogenomic APOLLO program, our serum repository DoD Framingham studies, and our toxin exposure research (PROMETHEUS)

- Partnerships with our world-class non-Federal entities including the Lawrence J. Ellison Institute for Transformative Medicine in California (represented here today by Dr. Jerry Lee) and many other partnerships to include the Chan Soon-Shiong Institute of Molecular Medicine at Windber, Molecular Institute at Windber, Pennsylvania, the American Genome Center of USUHS, Research Pathology Center of USU and INOVA Health, the Joint Pathology Center, and the personal relationship with the Murtha family

I first heard of Congressman Murtha in 1999 when I was unexpectedly called down to the Commander's office at the old Walter Reed Army Medical Center to be told that some Congressman put and earmark into the DoD budget for fiscal year 2000 that had some money in it for breast cancer research. Additionally, as a newly minted LTC, I was being 'voluntold' that it was my job to figure out what to do with it. I'll never forget the single sentence of sage advice that the general officer gave me in that office that day regarding my new duties to which I had no training. He only advice was, "Don't end up on the front page of the Washington Post." He didn't mean it in a good way, either. Twenty-three years and a career later, here we are celebrating the 10th anniversary of the namesake Cancer Center of that legendary giant of a man Congressman John P. Murtha.

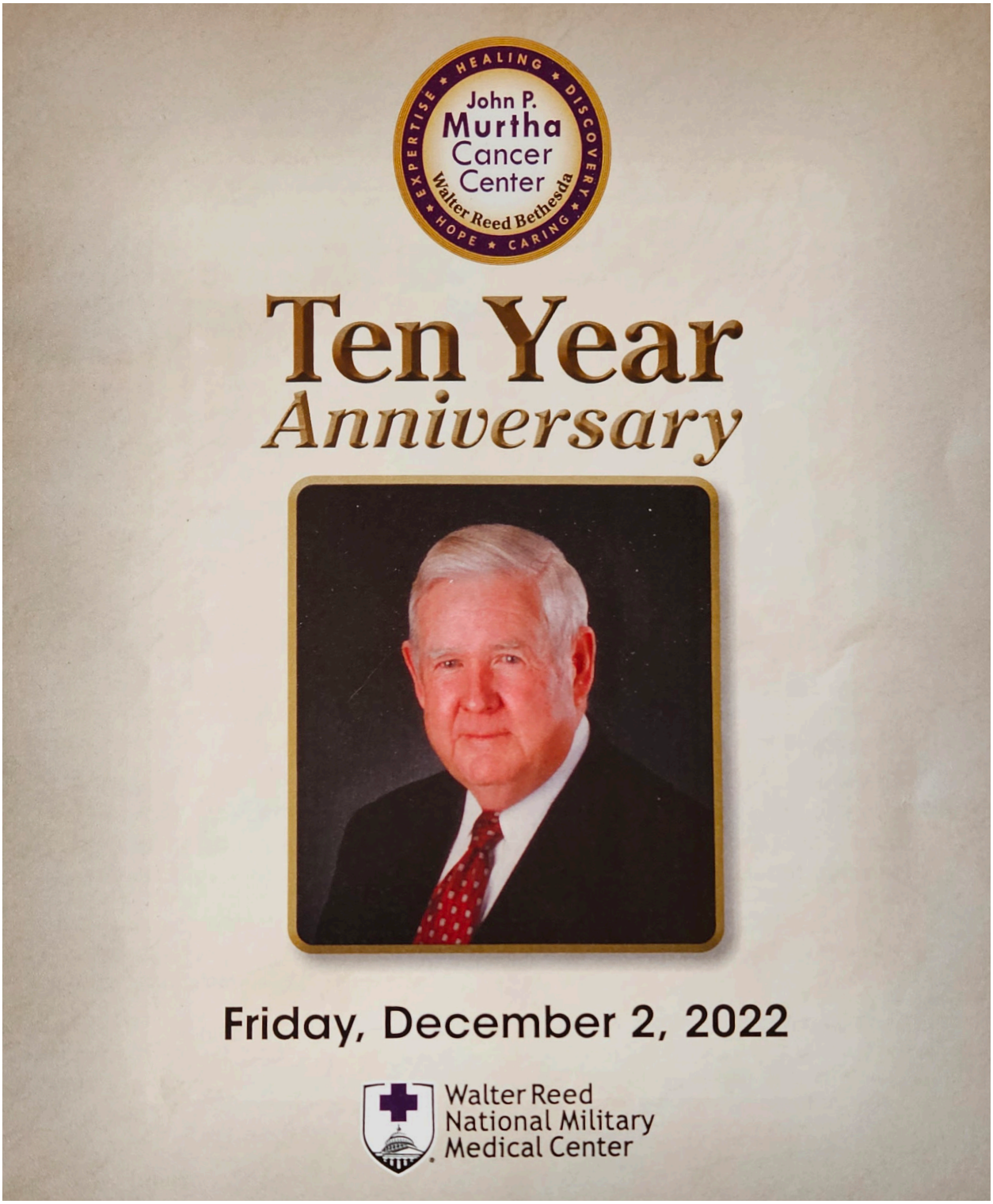
Over the intervening years, I personally met with him, briefed him, attended public events where he was speaking, and held private meetings with him in his office, along with the Army Congressional liaison of course, dozens and dozens of times. I also got to meet his family, his lovely wife Joyce, and other family members and forged an immutable bond that exist until this day. Though the years I learned to understand what the Congressman desired to be done with the resources that he generously directed into our efforts. And, everything that this Cancer Center does, sponsors, aspires to, enables, and carries out is just what he wanted. For he wanted his life and his legacy to be all about helping service members, veterans, beneficiaries, all people and specifically those people with cancer and being able to do research lessen the burden of the disease of cancer on people.

And so, on this 10th anniversary of the Murtha Cancer Center, I stand before you with one central feeling – a feeling of gratitude. Gratitude for all of you present here who are the reason why this vision of Congressman Murtha has been successful. Every single one of you who in positions of authority have enabled vision of helping our service members, veterans, and beneficiaries with cancer. All of you senior leaders and executives, directors, commanders, staff, agency leaders, deputies, funders, federal government officials, and civilian partners – All of you here, are why we are here. When I spoke to Mrs. Joyce Murtha last week, she asked me to tell you all, "Thank You". And, of all of the things that the Congressman did in his life the cancer program here and this Center would be his most proud legacy because it helps our people. At almost every event that I heard Congressman Murtha speak, he often relayed a story that his grandmother would always tell him, 'Jack, one person can make a difference'.

So, 12 years after his passing and 10 years after the founding and naming of the Murtha Cancer Center and thanks to all of you in this room who share his passion for helping people and those of you that share his passion for helping others are still making a difference. You are making a difference for the betterment of our patients, for the research findings and knowledge to better understand and ultimately defeat cancer, for the support of the ready medical force, and the overall enhancement of the readiness of the force.

So, on behalf of all our patients, past, present, and future, who have benefitted and will benefit from the clinical and research work done under this banner of the Murtha Cancer Center Research programs, I offer to each and every one of you my deepest thanks and sincerest gratitude.

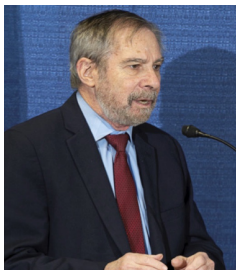
MURTHA CANCER CENTER AND MURTHA CANCER CENTER RESEARCH PROGRAM CELEBRATING 10 YEARS AS THE DOD'S CENTER OF EXCELLENCE FOR CANCER CARE



10TH ANNIVERSARY OF THE MURTHA CANCER CENTER AND MURTHA CANCER CENTER RESEARCH PROGRAM PROCLAMATION

Steven Lieberman, MD
Deputy Under Secretary for Health, VA

Seileen Mullen
Acting ASD(HA)



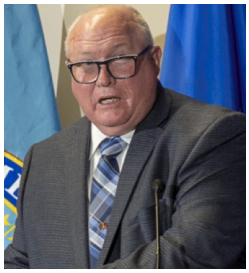
Douglas Lowy, MD
Principle Deputy Director, NCI

LTG Ronald Place, Director, DHA on behalf of Chairman, JCS

Johnathan Woodson, MD
President, USUHS

Captain Drew Bigby, MSC, USN
Interim Director, WRNMMC

Craig D. Shriver, MD
Director, MCC/MCCRP



Colonel Brian Murtha
USMC, Retired

THE MURTHA CANCER CENTER PERFORMING TRANSLATIONAL RESEARCH FOR MILITARY RELEVANT CANCERS

The John P. Murtha Cancer Center (MCC) was established originally at the Uniformed Services University of the Health Sciences (USU) as the United States Military Cancer Institute (USMCI) in 2002, becoming the MCC in 2012 with the completion of the Base Realignment and Closure (BRAC) 2005 process. On 22 May 2012, the MCC was designated as the Department of Defense (DoD) Center of Excellence for cancer care and research by the Assistant Secretary of Defense (Health Affairs) (ASD (HA)) Military Health System (MHS) Centers of Excellence Oversight Board. The MCC is a cancer research and treatment center at Walter Reed National Military Medical Center (WRNMMC).

The Murtha Cancer Center Research Program (MCCRP) integrates USU with the MCC to provide robust tri-service clinical cancer research integrated within National Capital Region (NCR) and throughout the MHS in three multidisciplinary translational cancer research programs: Center for Prostate Disease Research (CPDR), GYN Center of Excellence (GYN CoE) and the Clinical Breast Cancer Project (CBCP).

The MCCRP focuses on research designed to address cancer prevention, screening, treatment, rehabilitation, and survivorship of service members (SM), beneficiaries, and veterans who suffer from cancer, including translating research and development (R&D) into novel and innovative treatment and rehabilitation options. The DoD Joint Requirements Oversight Board approved the Initial Capabilities Document (IDC) for Cancer Care in 2017. The IDC resulted from the Cancer Care Capabilities-Based Assessment and established that the ultimate MCC goal for the MHS is that cancer is prevented, screened for, detected, treated, cured, and rehabilitated, or impacts of cancer and cancer treatment are mitigated so SMs are returned to duty, re-classified to a new duty position, or reintegrated into civilian/VA life with highest possible quality of life. MCCRP's cancer educational and clinical research capabilities are designed to enable the MHS to effectively and efficiently support a medically ready force and provide world-class cancer services for the MHS.

BREAST CANCER CENTER OF EXCELLENCE/ CLINICAL BREAST CARE PROJECT (CBCP)

The CBCP provides a multidisciplinary approach as the standard of care for treating breast diseases and breast cancer. This approach integrates prevention, screening, diagnosis, treatment and continuing care, incorporation of advances in risk reduction, biomedical informatics, tissue banking and translational research. The project is based on a discovery science paradigm, leveraging high-throughput molecular biology technology and our unique clinically well-characterized tissue repository with advances in biomedical informatics leading to hypothesis-generating discoveries that are then tested in hypothesis-driven experiments.

Breast cancer is the second leading cause of cancer death in women in the United States. The readiness and lethality of the Total Force is based in large part on personnel health. Nearly 20% of the active-duty force is now female, and breast cancer is the number one cancer in active-duty women, far surpassing all other causes of cancer in this population. The Breast Cancer CoE utilizes a multidisciplinary approach for researching breast diseases and breast cancer focused on the military at-risk active-duty population in order to enhance Readiness of The Total Force. This multidisciplinary model integrates prevention, screening, early diagnosis, treatment and continuing care. The project is further unique in the incorporation of advances in risk reduction, biomedical informatics, tissue banking and translational research. The project is based on a Discovery Science paradigm, leveraging high-throughput molecular biology technology and our unique clinically and pathologically well-characterized tissue repository with advances in biomedical informatics leading to hypothesis-generating discoveries that are then tested in hypothesis-driven experiments.

Key 2022 CBCP Accomplishments

- Accrued 187 new donors who contributed biospecimens at CBCP sites to the core tissue protocol this fiscal year.
- Accrued greater than 3,800 new biospecimen components at CBCP sites to the core tissue protocol this fiscal year.
- The program reached 10,000 cumulative donors in Breast Cancer CoE biobank, totaling 10,073 to date.
- The program has obtained greater that 228,068 cumulative aliquots from all donors.
- Published Biospecimen Science Research paper in PLOS One that addresses RNA quality issues.
- Utilized the program's biospecimen and data in support of 28 research publications this fiscal year.
- Accrued greater than 235 breast patients to CBCP core protocols
- Performed critical research on young women with breast cancer, key cohorts affecting cancer as a readiness issue for the DoD. Developed additional research work with NCI which further evolved into APOLLO 4C (Breast) comparing molecular features of tumors from young women with matched older women. Finished data collection from proteogenomic platforms, and cohort level analyses are well underway, towards a manuscript which structure has been decided.
- The Massive Parallel Multiple Processing project is reaching the final stage of analysis to understand the molecular characteristics of difficult-to-treat subtypes of breast cancers, and manuscript preparation has started.
- A study of breast cancer margin status using The Cancer Genome Atlas Program (TCGA) and CBCP data is wrapping up with an abstract presented at American Association of Cancer Researchers (AACR) 2022, and the manuscript is in preparation.
- Progress is made in TCGA treatment data analysis with an abstract presented at AACR 2022. The competing priorities for the analysis capacity is limiting the progress of this project, but significant headway has been made in treatment response and gene signature analyses.

PROSTATE CANCER CENTER OF EXCELLENCE/ CENTER FOR PROSTATE DISEASE RESEARCH (CPDR)

The Center for Prostate Disease Research (CPDR) is the DoD designated Prostate Cancer Center of Excellence (CoE) conducting interdisciplinary translational cancer research program of the Murtha Cancer Center, Department of Surgery, USU and the Walter Reed National Military Medical Center (WRNMMC). The CPDR conducts state-of-the-art clinical, translational and epidemiology research with emphasis on precision medicine to enhance the readiness of active-duty personnel in conjunction with the continuum of medical care for military retirees and beneficiaries. Ground-breaking discoveries through strong academic and clinical research (e.g., 30 yrs. and over 450 publications) have led to major advances in translational prostate cancer research and treatment. The CPDR integrates expertise of urologic and medical oncologists, cancer biologists, genitourinary pathologists, epidemiologists, biostatisticians, medical technologists, research nurses, patient educators, and program management specialists. All these areas of expertise provide state-of-the-art resources for in-house and collaborative research in prostate cancer. The CPDR enriches the training of the next generation of physicians/scientists who directly benefit the quality, outcomes, and stability of the military health care delivery system.

CPDR is at the forefront of "cutting-edge" translational, clinical, and epidemiologic prostate cancer research. The emphasis is on improving prevention, diagnosis, prognosis and treatment of prostate cancer involving new modalities such as MRI guided biopsy, gene-based biomarkers, and precision medicine strategies targeting cancer-causing alterations in prostate cancer. The CoE multi-center database (WRNMMC, NMCSD, BAMC, MAMC, TAMC) is a unique programmatic resource, enrolling over 30,500 DoD health care beneficiaries with longitudinal follow up to

30 years. Research from CoE highlights genetic and genomic racial/ethnic differences, discovery of novel prognostic markers, treatment outcomes, and new insights into quality of life.

The CPDR's health disparity research focus has uniquely benefited from studying prostate cancer patients in DoD with high representation of African American men, in an equal-access military health care system. CPDR has been credited for the discovery of the frequent overexpression of the most common prostate cancer driver gene, ERG, the development of urine assay and tissue assay to detect ERG; the discovery of tumor genomic differences between African American and Caucasian American patients; and the discovery of inherited gene mutations that drive aggressive prostate cancers of African American men. The CPDR's state-of-the-art research infrastructure and framework is providing education and training for over 100 next generation physicians, scientists, medical and graduate students within DoD medical institutions.

Key 2022 CPDR Accomplishments

- CPDR's Clinical Research Program at WRNMMC, combines a multidisciplinary approach of prostate cancer screening, data collection, clinical diagnosis, and treatment, education and counseling, and prostate disease clinical trial research in an efficient, personal- and patient-oriented manner.
- The program continues to advance collaborations with NCI-Medical Oncologists to enhance treatment of advanced prostate cancer patients at WRNMMC.
- CPDR has enrolled patients in clinical trials for more than two decades. Currently, there are five clinical trials for immunotherapy, cancer vaccine, and advanced prostate cancer therapy ranging from prevention to quality-of-life.
- The Clinical Program collects serum, urine, tissue specimens (WRNMMC) through the integrated MCC biospecimen bank and patient data through the multicenter national database (WRNMMC, NMCSD, BAMC, MAMC, TAMC).
- The CPDR prostate cancer bio-specimens bank currently houses over 200,000 units of various types of specimens which are driving engines of ground-breaking discoveries.
- Highlights of the Clinical Research program accomplishment include new findings in race-specific prostate cancer outcome of MHS beneficiaries, quality of life assessment following robotic surgery, machine learning to estimate 10-years survival of patients with bone metastasis, impact of race and age on quality of life, and a new formula to estimate patient's health in prostate cancer counseling.
- CPDR Translational Research Program continues to discover prostate cancer-causing gene defects, biomarkers for the screen-detection and prevention of aggressive prostate cancer and to develop new inhibitors of disease progression.
- The CPDR Translational Research Program discovered that prostate cancer patients of African ancestry frequently inherit gene mutations of the DNA damage repair genes (RAD genes aka BRCA1/2-containing complex subunit genes). Like the breast cancer BRCA1/2 genes, RAD gene mutations are potential targets for PARP inhibitor therapy, Nature Communications, Mar 15;13(1):1361, 2022.
- CPDR had major contributions to establishing new polygenic hazard scores and to highlight genetic risk predictors of rare inherited gene variants increasing the prostate cancer risk of men of African ancestry, Prostate Cancer Prostatic Dis. 2022 Feb 12, 2022; European Urology May;81(5):458-462, 2022.
- FDA designated as breakthrough device the ExoDx Prostate (EPI) test that is the CoE's urine exosome prostate cancer screen panel licensed earlier to Exosome Diagnostics and now reimbursed by Medicare, CareFirst, BlueCross and BlueShield and Humana. The test has been incorporated into the National Comprehensive Cancer Network guidelines.
- CPDR has recently developed a new formulation of the ERG oncogene inhibitor, ERG-USU-6 formula #16 with improved solubility and bioavailability for inhibiting the growth of ERG positive prostate cancer that represents 50% of all primary prostate cancer cases. Further, the CoE contributed to a publication on a new inhibitor of castration resistant prostate cancer through the glycolytic regulation, Eldhose et al., ACS Med Chem Lett Oct 19;12(11):1703-1709, 2021; Dylgjeri et al., Clin Cancer Res Apr 1;28(7):1446-1459, 2022.

GYNECOLOGIC CANCER CENTER OF EXCELLENCE (GYN COE)

The Gynecologic Cancer Center of Excellence (GYN-CoE) utilizes a program project type of strategy with overarching objectives to advance knowledge, prevention strategies, companion biomarkers and assays, treatments and interventions across the continuum of care in gynecologic oncology. GYN-CoE's twelve program projects run in parallel rather than in sequence with advances implemented over five years rather than 12 months. Some subprojects target discovery investigations and mechanistic studies whereas others focus on clinical evaluations, population studies and further development leading to deployment. The introduction of new subprojects and maturation of other subprojects allows the GYN-CoE to continue to emphasize military and clinical relevance, prioritize bench to bedside translation, and infuse in advances in science, medicine and technology to meet it's objectives.

The GYN-CoE is an integrated translational research program aimed at development of companion biomarkers and assays, clinical decision support tools, risk assessment algorithms, quality improvement initiatives, treatments, and interventions for patients with gynecologic tumors and cancers, among a growing proportion of active duty women in the Armed Services, veteran and retired populations. Molecular profiling of pre-cancerous and malignant lesions has also enabled development of diagnostic and chemo-preventive interventions across the most common pathologic uterine conditions, rare variants, and the aggressive and deadly metastatic and recurrent malignancies that affect women and corresponding readiness. The GYN-CoE has been the leading research program in the U.S. to identify clinical features, biologic etiologies, and social determinants underlying racial and ethnic disparities in gynecologic cancers using population based as well as translational research methods. The GYN-CoE program features both the largest tissue laser capture microscopy facility as well as the most robust mass spectrometry-based proteomics facility in the DoD, enabling the program to assess the generalized relevance of GYN-CoE discoveries in other cancers that impact service members and readiness. The comprehensive research program supports the training of subspecialty gynecologic oncology surgeons, a fellowship program that has trained advanced pelvic surgeons to support wartime efforts for the past 50 years. The program also educates and trains medical students, interns and residents in women's health, telemedicine, wellness, wound-healing, hemorrhage, infections, pain management, resistance, resilience, palliative care and evidence-based medicine. The program has partnered with the National Cancer Institute in its educational and investigative activities over the past 20 years becoming a pillar program for the MCCRP and the USU. The GYN-CoE has also strengthened cancer capabilities, advanced the federal precision oncology initiatives, contributed to the COVID-response, enabled delivery of equitable care to female service members, veterans and beneficiaries, and ensured readiness of the female fighting force by addressing their gender-specific medical conditions.

The GYN CoE focuses on characterizing the molecular alterations associated with benign and malignant gynecological disease and facilitates the development of novel early detection, prevention and novel biologic therapeutics for the management of gynecological disease. The GYN-CoE leverages innovative research to enhance gynecologic cancer care from prevention to survivorship for service members, beneficiaries, and the civilian population.

Key 2022 GYN CoE Accomplishments

- Biological Investigations and Molecular Profiling of Gynecologic Cancers.
  - Quantitative proteomic analysis revealed unique proteome alterations in post versus pre-neoadjuvant chemotherapy (NACT) tumors from patients experiencing excellent or poor NACT response. The alterations may enhance treatment decisions and rationale for selecting alternative therapy in those with poor response to NACT.
  - Proteomic Analysis of Acquired Chemoresistance and End Stage Disease from the Largest Ovarian Cancer Autopsy Cohort in the World was finalized. The preliminary bioinformatics analyses have been completed and evidence for of a necrotic or hypoxic proteomic signature suggests that the autopsy specimens are not dominated by these potential artifacts. Bioinformatic analyses will continue with the goal of identifying patterns of chemoresistance in end-stage ovarian cancer.
- Racial and Ethnic Disparities.
  - Uterine leiomyomas (ULMs) are the most common tumor of the female genital tract. Prevalence of ULMs is higher in African-American (AA), who also experience greater severity of symptoms and different responses to treatment than Caucasian (CA) women. Quantitative analyses revealed transcriptome alterations correlating with altered estrogen receptor (ESR) and progesterone receptor (PGR) signaling, altered tumor growth factor beta (TGFB) expression as well as distinct proteomic changes among White and Black ULMs, providing insight into the pathogenesis of disparities seen in this common disease. These findings may also clarify novel therapeutic strategies that support individualized treatment.
- Refining Military Clinical Support Capabilities in Adolescent/Young Adults versus Older Adults with Cervical Cancer: An Investigation of Cancer Health Disparities using the National Cancer Database
  - Young women with cervical cancer are a clinically unique subset of patients that have different clinical and prognostic factors that affect survival outcomes. The Adolescent/Young Adult (AYA) cohort had a lower comorbidity score, higher percentage of Hispanic women, lower tumor grade, earlier stage disease, and were more likely to undergo surgical treatment. Understanding the differences will improve cervical cancer care in the Military Health System. In addition, the 14% risk of death at 2 years in the AYA group emphasizes the importance of HPV-vaccination for prevention of all HPV-related cancers including cervical cancer and adherence to thorough screening to mitigate the high cancer-related mortality in young adults and enhance return to duty keeping our female service members in the fight.
- Racial Disparities in High-Risk Uterine Cancer Histologic Subtypes: A United States Cancer Statistics study.
  - Black women have a two to four-fold higher incidence of high-risk uterine cancer subtypes, particularly serous carcinoma, carcinosarcoma, and leiomyosarcoma, compared to White women after correcting for hysterectomy and active pregnancy.
- Comprehensive Proteogenomic Analyses of High-grade Serous Ovarian Cancer.
  - Although many studies including TCGA select for pure tumors to enhance detection of cancer-related biomarkers, many impure tumors are associated with poor prognosis raising selection bias concerns. Inclusion of all cancer patients irrespective of tumor purity with use of enrichment techniques to prepare tumor micro-compartments was aligned with comprehensive proteogenomics in an advanced stage high grade serous ovarian cancer (HGSOC) patient cohort toward identifying novel and clinically relevant alterations previously unreported. The study data demonstrate the feasibility of conducting cohort-level proteogenomics of the tumor microenvironment; highlight novel findings that should be correlated with response to DDR and checkpoint inhibitors in clinical trials; and establishes a non-restrictive paradigm for patient inclusion and specimen prep in support of the prospective mission-scale analyses associated with APOLLO.

In 2022 the Murtha Research Network grew to 10 Military Treatment Facilities, 7 Veterans Affairs Medical Centers, 1 Civilian Medical Center and a Consolidated Biorepository.

MCCRP biobank protocols have become the platform on which the Murtha Research Network is being built. The specimens and data that are collected from volunteers at the Network's sites will be used in MCCRP facilitated scientific collaborations to help prevent, diagnose, treat and cure cancer, in SMs and DoD beneficiaries. In 2022, 1,535 patients were consented to participate in MCCRP/MCCRP specimen collection protocols and 764 patients voluntarily donated specimens to the biobank. The figure below depicts the present sources of the biospecimens, shipping and consolidation site, and potential research use sites.

In the past decade, it has become increasingly clear that access to human tissue is the most critical component of successful biomedical research aimed at cancer detection, prevention and cure. It is undeniable that the development of future targeted cancer interventions will require broad access to this scarce resource of uniformly collected and stored human specimens linked to a detailed epidemiological database. The MCCRP is building a military-based tissue repository of prospectively collected biospecimens that will fulfill the research needs of DoD investigators and their collaborators. A master template for implementation at participating sites in the Murtha Research Network has been developed. This protocol establishes strict guidelines and procedures for biorepository efforts and formulates the processes necessary for the highest quality tissue collection, storage and distribution. Collected biospecimens will be used in all types of research and development, such as finding the cause of disease, developing new diagnostic tests, or advanced approaches to treatments and cures. The biospecimens may also be used in genetic research or research into hereditary diseases. They will be used by DoD, VA and NCI researchers and collaborators and other DoD funded projects such as APOLLO and ORIEN.

MILITARY CANCER BIOREPOSITORY

On April 29, 2022, MCCRP celebrated the 10,000th Clinical Breast Care Project patient donor's biospecimen contribution to the DoD consolidated CAP-accredited biorepository at the Chan Soon-Shiong Institute of Molecular Medicine at Windber, PA. There have been over 90,000 research grade biospecimens collected from these 10,000 donors and stored at the biorepository since 2002 for use in cancer research.

In 2022 the Cancer Biorepository contained 526,368 aliquoted biospecimens from 26,354 consented donors. Windber Research Institute as Chan Soon-Shiong Institute of Molecular Medicine at Windber was founded in the year 2000, with the inception of the CBCP. CBCP is a U.S. Congress mandated research program resourced by the late Congressman John P. Murtha. There are five pillars of the CBCP and our Institute is responsible for Biobanking, Biomedical Informatics, and Focused Research activities. Clinical Care and Risk Reduction are led by the clinical teams spearheaded by the MCCRP of the Uniformed Services University of Health Sciences. The Institute has over the years supported other major research programs of the Department of Defense including a cardiologic disease study, a gynecologic disease program, and pan-cancer studies. The Institute has since developed its expertise in biobanking and biorepository sciences, informatics infrastructure system development, bioinformatics, and translational research in breast cancer. Our biobanking and infrastructure systems are now supporting major consortium research programs such as the Applied Proteogenomic OrganizationaL Learning and Outcomes (APOLLO), as well as the Oncology Research Information Exchange Network (ORIEN) as part of the MCCRP. Our research has provided insights into the understanding of breast cancer racial disparity, breast cancer in young women, and the importance of high-quality clinical data in cancer studies.

The specimens in the biorepository are especially relevant to the military. They provide researchers with the opportunity to investigate frequent or unusual tumors arising in military populations and determine if these cancers are related to occupational exposure or other common stresses. They provide the opportunity to investigate carcinogens specific to military settings and determine their relationship to tumor development. The active duty military population is unique in its potential for exposure to dangerous chemicals, inhalants, biological agents, and nuclear contaminants. Military personnel are subjected to extremely stressful situations and environments. They are often cohabitants and function as a unit, resulting in a host of shared environmental experiences among large populations deployed to the same area. As such, they may develop consequences of these exposures as a group. The repository provides researchers with the opportunity to identify tumors that may be related to occupational or environmental exposures or other military settings and determine their relationship to tumor development. The benefits of these research specimens include improving our overall understanding of cancer and other disease

processes as they relate to the military population and beneficiaries, developing a new generation of biomarkers for early detection of cancer, and developing new therapeutic regimens for cancer treatment. Future diagnostic and treatment efforts may be aided by the availability of these stored tissues and specimens. As newer molecular techniques evolve for evaluating tumors, investigators may begin to make sense of activities at a molecular level far in the future from the time of tissue collection.

APPLIED PROTEOGENOMICS ORGANIZATIONAL AND LEARNING (APOLLO) NETWORK UPDATES

MCCRP researchers have discovered a molecular predictor of lung adenocarcinoma survival.

The Applied Proteogenomics OrganizationaL and Learning (APOLLO) Network represents an important interagency partnership that brings together the scientific and technical capabilities of NCI, DoD, and VA to create the nation's first healthcare enterprise where proteomic analysis complements genomic sequencing in cancer patients to inform targeted therapy decision making. This collaboration establishes a new paradigm that merges the silos of research expertise and clinical care improvement to enable an environment of rapid iterative learning and direct implementation into clinical care. The unique capabilities of each member of this tri-agency coalition synergize to accelerate the pace of discovery, prospectively validate those findings in defined patient cohorts, and disseminate generalizable results as best practices and guidelines for adoption across a healthcare system. By combining resources, intellectual capacity and technologies in research, clinical care, and information dissemination in an integrated manner, the NCI. DoD, and VA are poised to provide a model of cancer care for the entire nation. Below is a full list of APOLLO studies:

APOLLO 1 = Lung cancer; APOLLO 2 = Gynecological cancer; APOLLO 3 = Prostate cancer; APOLLO 4 = Breast cancer; and APOLLO 5 = prospectively collected VA, DoD, and NCI specimens and data for all organ sites, APOLLO 6: Pancreatic Cancer and APOLLO 7 (Protocol in development): Testicular Germ Cell Tumors and APOLLO 8 (Protocol in development): Malignant Brain Tumors/glioblastoma (GBM) cases.

There were remarkable results in APOLLO 1 in 2022. Lung adenocarcinoma (LUAD) is one of the greatest causes of cancer deaths, and displays wide ranging heterogeneity: clinically, morphologically, molecularly, genetically, challenge for prognosis and treatment for all patients. Genome-wide profiling has described molecular variation in the transcriptome and exome of LUAD and few recent studies have emerged on whole genome and proteomics variation, or proteogenomics. MCCRP scientists applied proteogenomics to a well clinically annotated cohort, to enable deeper molecular characterization of LUAD, leading to a better diagnosis, and better estimation of clinical outcomes (e.g., identify prognostic biomarkers).

The first, large proteogenomic characterization of Lung adenocarcinoma (LUAD) from the United States population and corresponding smoke exposure were generated. Using six molecular profiling technologies, four layers of LUAD biology: whole genome, transcriptome, proteome, and phosphor-proteome were measured. Through systematic analysis of these proteogenomic data, major alterations, molecular subtypes, signaling patterns in LUAD tumors were identified. Combined analysis with thorough 5 year clinical follow-up data enabled the identification of proteogenomic discriminants of long- and short-term surviving individuals with LUAD.

APOLLO RETREATS

APOLLO RETREAT
Murtha Cancer Center Research Program
Friday, April 1, 2022

APOLLO RETREAT
Murtha Cancer Center Research Program
September 22-23, 2022

APOLLO Retreat
Thursday, 22 September 2022
In person: 56
Virtual: 133
Total: 189

APOLLO Retreat
Friday, 23 September 2022
In person: 56
Virtual: 120
Total: 176

FRAMINGHAM UPDATES

The Framingham research collaborations have discovered a 13-protein classifier that is highly promising for detection of OPSCC prior to overt symptoms.

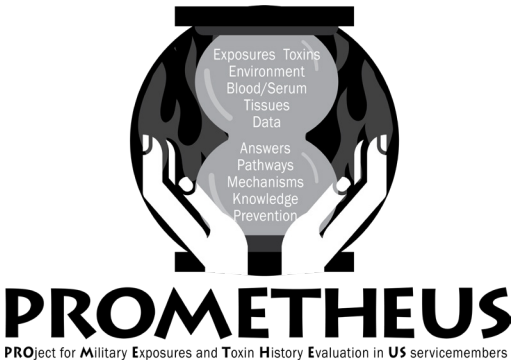
In the Framingham series this fiscal year, the new Framingham 1B validation study was included. Framingham 1B looked to validate the biomarker panel that was developed in an earlier DoD Framingham study for oropharyngeal squamous cell carcinoma (OPSCC). In this new Framingham project 1B, the proven attributes of the DoD Serum Repository maintained by AFHSD to validate the novel diagnostic protein biomarker panel that we developed in earlier Framingham, in the serum/blood of service members were used. Through a subaward with Batelle and Pacific Northwest National Laboratory (PNNL), high-level mass spectroscopy-based proteomics of a series of blood serum samples drawn from a new cohort of active duty service members diagnosed with OPSCC while on active duty, with data created for each individual sample collected, recorded on PNNL's instruments, named according to the randomized identifier assigned to the sample, and stored on PNNL's secured proteomics data servers were performed. PNNL performed dissemination of data to internal (PNNL) analysts to perform high-end big data statistical analysis. The PNNL Bioinformatics team examined whether any of the target peptides or group of peptides can be distinguished between the patients and their matched controls for each specific aim of this study based on the protein panel we previously described. The PNNL bioinformatics team also performed comparative analysis of serum markers of OPSCC patients to cancer-free controls at points prior to diagnosis, during the course of treatment, and during post-treatment surveillance. This project represented a unique opportunity to leverage the Department of Defense's (DoD's) cancer registry and serum repository to identify linkages between pre-diagnostic biological markers, markers of response to treatment and outcomes, for a number of militarily relevant cancer. The Department of Defense Serum Repository (DoDSR), maintained by the Armed Forces Health Surveillance Division (AFHSD) in Silver Spring, Maryland, is a biological repository of human serum contained within large-scale freezers operated by the DoD containing over 64,000,000 (64 million) serum specimens collected from over 10 million past and present members of the United States Armed Forces while on active duty.

MOONSHOT 2.0

On 2 February 2022 Biden-Harris Administration set goals of reducing cancer death rate by at least 50 percent over the next 25 Years and improving the experience of living with and surviving cancer. The President and First Lady reignited the Cancer Moonshot and formed the first-ever Cancer Cabinet to mobilize all levers of the federal government and realize the President's vision of ending cancer as we know it. In July 2022, the Cancer Cabinet unveiled priority actions to: (1) close the screening gap, (2) understand and address environmental exposure, (3) decrease the impact of preventable cancers, (4) bring cutting edge research through the pipeline to patients and communities, and (5) support patients and caregivers.

PROJECT FOR MILITARY EXPOSURES AND TOXIN HISTORY EVALUATION IN U.S. SERVICE MEMBERS (PROMETHEUS)

In 2022 the MCCRP has reviewed 32 research proposals from several research activities to gain an understanding of the impact of service-related toxic exposure on the development of cancer in members of the military.



In Greek mythology, Prometheus is a Titan god of fire. Prometheus is best known for defying the gods by stealing fire from them and giving it to humanity in the form of technology, knowledge, and more generally, civilization. In some versions of the myth, he is also credited with the creation of humanity from clay. Prometheus is known for his intelligence and for being a champion of humankind and is also generally seen as the author of the human arts and sciences.

The DoD Cancer Cabinet leaders announced the creation of a research program to understand military toxic exposure. The Department of Defense's Murtha Cancer Center Research Program has launched a new program with the goal of understanding the impact of service-related toxic exposure on the development of cancer in members of the military. PROMETHEUS, or the PROject for Military Exposures and Toxin History Evaluation in U.S. service members will bring together agency and private sector innovators to understand and address cancer in exposed service members. It brings together significant DoD capabilities including the DoD Serum Repository which contains blood samples for all service members; the Individual Longitudinal Exposure Record (ILER) which tracks toxin exposures; the DOD Tumor Registry which tracks cancer diagnoses in active duty; DoD Framingham which analyzes blood proteins in active duty with cancer; the Joint Pathology Center which is the DoD's pathology center of excellence; and APOLLO, which was created in response to the Cancer Moonshot in 2016 now with a network of 13 hospitals to carry out military-specific research.

PROMETHEUS will integrate federal scientific platforms with public-private innovators to study the impact of service-related exposures to environmental contaminants and toxin hazards. PROMETHEUS' goal is to discover advanced precision oncology technologies that will enable prevention, early detection, and enhanced treatments of cancers arising from these exposures so military service members are returned to duty, re-classified to a new duty position, or reintegrated into civilian/Department of Veterans Affairs (VA) life with the highest possible quality of life. PROMETHEUS will create a process and research ecosystem to integrate or link individual-level datasets of exposures and phenotypic information and conduct research studies that leverage exposure data, phenotypic data, and biospecimens, which are unique to DoD military service members and veterans. PROMETHEUS will integrate scientific platforms of the Department of Defense (DoD), VA, Department of Energy (DOE), Pacific Northwest National Laboratory (PNNL); National Institutes of Health (NIH), especially the National Cancer Institute (NCI) and the National Institute of Environmental Health Sciences (NIEHS); and other federal, civilian, and academic entities to meet these challenges.

PROMETHEUS will incorporate several of the precision oncology programs that evolved from the first Cancer Moonshot as well as new important public-private collaborations:

- APOLLO (Applied Proteogenomics OrganizationaL Learning and Outcomes) was the first DoD program to emerge from the original Cancer Moonshot program, based on a collaboration between DoD, VA, and NCI for translational proteogenomics research. DoD Framingham Longitudinal Molecular Cancer Study - researchers are identifying new linkages between pre-diagnostic biological markers and various types of cancer.
- The Post Deployment Health Services/Health Outcomes of Military Exposures, a VA-Delivered Core Service, assesses the impact of deployment and environmental exposures on veterans and develops related policy, research, education, and healthcare strategies.

- DOE PNNL and DoD collaborations have novel mass spectrometry capabilities that have been applied to various DOE and NCI biology questions.
- The Individual Longitudinal Exposure Record (ILER) is a web application that compiles, collates, and presents available occupational and environmental exposure information in a individual/person-centric format.
- MCCRP Military Cancer Clinical Trials and Research Network the source of Multi-Federal Biospecimens and Data and link to cancer clinical trials
- MCCRP Advanced Research Technologies – Proteogenomics Proteogenomic profiling capabilities offered by the APOLLO collaboration provides an unprecedented opportunity for advancement in the development of diagnostic tests and treatments targeted to the unique molecular properties of individual cancers.
- MCCRP Central Cancer Biorepository and Data Center. MCCRP biobank protocols establish platform on which the Military Cancer Clinical Trials Network is built. The specimens and data that collected from volunteers at the Network's sites are used in MCCRP to facilitate scientific collaborations that will prevent, diagnose, treat and cure cancer, in Service Members and DoD beneficiaries.
- Applied Proteogenomics OrganizationaL Learning and Outcomes (APOLLO) Providing state-of-the-art molecular analysis of tumors and blood of cancer patients which will result in increased force readiness through more targeted treatment of cancers with fewer side effects, as well as better screening for cancer risk and development.
- DoD Framingham - Longitudinal Molecular Cancer Program. A retrospective analysis of longitudinal serum samples collected over the course of the subjects' military active component service. Cutting-edge proteomics research is being used to identify serum biomarkers indicative of disease states to develop early diagnostic tools and prognostic indicators, which may be used to inform treatment decisions and improve survival. This study is comparing serum markers of active duty cancer patients to cancer-free controls at points prior to diagnosis, during the course of treatment, and during post-treatment surveillance.

PROMETEUS Scientific Planning Meeting | ***29 July 2022***
In person: 64
Virtual: 50
Total 114

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